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ANNALS OF
INTERNAL MEDICINE

VOLUME 25 SEPTEMBER, 1946 NUMBER 3

EVALUATION OF THE SEVERAL METHODS FOR TREATING GRAVES' DISEASE AVAILABLE TODAY *

By J. H. MEANS, M.D., F.A.C.P., *Boston, Massachusetts*

THE proof of the pudding is the eating, and similarly the proof of the treatment of any disease lies in the practice thereof, and that for a sufficient length of time and under adequately controlled circumstances. Forms of therapy ultimately survive or disappear in accordance with the impression they make on dispassionate, yet qualified observers. Time is a requisite in their appraisal.

The inventors of new remedies may often be classified as qualified, but not always as dispassionate. Since they are human, like the rest of us, complete objectivity with regard to their inventions is perhaps more than we have a right to expect of them.

I have been concerned with the appraisal of methods available for treating Graves' disease for most of my professional life. Since I am the inventor of none of them, I may lay claim to some objectivity in their evaluation.

The doctor, of course, should treat not only the disease but also the patient. Sometimes it is more important to treat the patient than his disease, but not so in the case of Graves' disease. In my somewhat long contact with this malady it has been my experience that except in rare instances, if you cure the disease you cure the patient. What I mean to say is that, although Graves' disease may be precipitated by shocking experiences, the imbalance which I believe the malady to be persists long after the provoking factor has gone, and the cure is to be found in the restoration to normal function of systems of the body whose derangement has outlasted what caused it. When the question has been: "Has this patient a psychoneurosis in addition to his Graves' disease?" our experience has been that usually when the thyrotoxicosis has been controlled the evidence of psychoneurosis disappears. There-

* Read at the Philadelphia meeting of the American College of Physicians.
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fore, I would say that in patients with Graves' disease, the doctor's chief job is to treat the disease.

What methods have we for doing this? In the past many drugs, iron, arsenic, digitalis, iodine, ergot, hydrocyanic acid, quinine, thyroid, and others have been tried in the treatment of Graves'; also other forms of treatment, such as prolonged rest, electricity, hydrotherapy, anti-sera, etc., have been used. None of these measures was of any great significance save iodine, and that had fallen into desuetude following Kocher [1] because of his pronouncements against it, until the late H. S. Plummer [2] reintroduced it in 1923.

The more modern methods of treatment which I wish now to appraise are as follows:

1. Subtotal ablation of the thyroid.
2. Antithyroid drugs.
3. Irradiation of the thyroid by means of radioactive iodine.

These various measures are used with the purpose of reducing thyrotoxicosis. There is another category of therapies which are designed to relieve the ophthalmic involvement when that is the more serious part of the picture. I have discussed these latter in a recent paper [3] and will not consider them further today.

The measures I have mentioned which are aimed at the thyrotoxicosis are sometimes used in combination. Thus surgical removal of the thyroid presupposes adequate preparation for operation, which nowadays, except in very mild cases where iodine alone may suffice, should include, unless a contraindication be encountered, the use of thiouracil or one of its relatives, and iodine. It is very important in appraising thyroid surgery to consider not only progress in operative technic and in anesthesia, but also in the specific preparation of the patient for operation.

I said in the beginning that the proof of a treatment is to be found in the practice of it. So now let me tell you that no longer than four years ago I attempted to identify the best treatment available for Graves' disease by surveying the ways in which we actually had treated it during a 25 year period.[4] I may say further that at that time I reached conclusions rather different from those I shall draw today, and those that I shall draw today are probably different from those that others may draw today or that I may draw tomorrow. The fact is that there are different schools of thougnt on this subject. When a therapy is introduced which converts a previously fatal disease into one completely relievable, like insulin in diabetes or liver in pernicious anemia, there are no different schools of thought as to how to treat the disease, except in the matter of details.

But this is not the situation in Graves' disease. In the first place, Graves' disease is not necessarily fatal. Even in the absence of all treatment, spontaneous recovery is quite possible. In the second place, we already had,

prior to the introduction of the latest forms of therapy, methods of treatment which on the whole were fairly satisfactory. Our problem, therefore, is to determine, if possible, which of *several* effective forms of treatment now available actually offers the patient the greatest chance of complete and lasting relief, and which subjects him to the least possible risk, inconvenience and expense. We also should discover whether in a certain type of case one method of treatment is preferable, while in another type of case a different method of treatment is to be preferred. Since Graves' disease may run a chronic course with spontaneous remissions and relapses, such an evaluation of methods of treatment is far from simple.

In my paper entitled "How We Have Treated Graves' Disease during a Quarter Century" published four years ago,[4] I pointed out that on the basis of that experience the conclusion seemed warranted that subtotal thyroidectomy following adequate preparation by a course of iodine offered more overall benefit than any other program then available. I pointed out also that in certain cases long continued exhibition of iodine alone had been found to be sufficient treatment. This last may still hold true occasionally.

At the onset of our studies in 1914, Aub and I [5] decided to test the relative merits of roentgen-ray treatment and surgery for Graves' disease. That was in the era before the routine use of iodine, and surgical mortality was rather appalling. For that reason non-surgical methods of therapy found much favor. I cannot go into the details now of how we compared roentgen therapy and surgical; it has all been published,[5, 6] but I may recall that our overall conclusions were that irradiation of the thyroid by roentgen-ray brought about an apparent cure in approximately one-third of the cases, benefit in another third, and no benefit in the remaining third. For a time, therefore, it was usual to use roentgen-ray treatment first, with the hope that it might be all that was needed, but operating later in most cases in which it failed.

In 1923, with the introduction of iodine and consequent decrease in operative mortality, subtotal thyroidectomy after preparation with iodine became the method of choice. Now in 1946, with newer forms of therapy available, the whole question of what is the best form of treatment for Graves' disease is again thrown wide open.

Before approaching this question directly, let us consider for a moment what contribution the newer methods may have made when used in conjunction with surgery. If one compares the preparation of the patient for operation by the administration of an antithyroid drug, such as thiouracil, with the older one of iodine alone, then it can be said that by thiouracil it is possible to deliver the patient to the surgeon more dependably in a euthyroid state than was ever possible by iodine.[7] But the use of thiouracil alone, all agree, gives the surgeon a very vascular gland in which hemostasis is difficult. However, it is also evident that by giving both thiouracil and iodine together,[8, 9] one can achieve the nearly perfect preparation. Not only is the

patient in a euthyroid state, but the thyroid gland is involuted and easy for the surgeon to deal with. The operative and immediate post-operative course in this group of patients so prepared is smoother and freer of complications than anything I have ever seen before. Following such operations it has been possible to omit both drugs the day of operation, and thus far in a series of 139 cases, we have seen only two persistences and no recurrences of thyrotoxicosis.

I am convinced by what we have observed in the short time since the antithyroid drugs were introduced, that they have materially improved the preparation for operation and consequently the risk of operation. One cannot say yet what effect the use of them will have on recurrences or relapses in the years to come.

Let us now observe how the results of prolonged treatment with an antithyroid drug alone compare with those of surgery at its best, and in the optimally prepared patient. Although antithyroid drugs have been in use for only three years, there is already a relatively huge literature on them. This was well digested and summarized up to December 1945 in an excellent review by Riker and Wescoe.[10] They give 105 references. In the *Journal of the American Medical Association* for February 9, 1946, there are reports of two surveys of the toxic effects of thiouracil, and an editorial. F. D. Moore [11] compiled data from 11 clinics on 1091 patients treated with thiouracil. W. D. Van Winkle, Jr., et al.[12] obtained information by questionnaire from 328 investigators on 5745 cases. More recently still, R. H. Williams [13] has reported very fully on his own large series of 247 treated cases, and Williams, et al.[14] have reported their toxic reactions.

This material permits it to be said categorically that thiouracil, if given long enough and in sufficient dosage, will produce a remission in any patient with Graves' disease, and that such a remission will continue as long as the drug is continued uninterruptedly. But the pay-off on all this is to be found in the toxic reactions, the recurrences after cessation of treatment, and the cases of aggravation of the ophthalmopathy. The last mentioned seem to be very rare and probably can be dismissed. Certainly they are on the low side of those encountered after thyroidectomy.

On the matter of toxic reactions we find from the papers mentioned above that fatalities attributable to drug are not over 0.5 per cent, agranulocytoses not over 2.5 per cent, and total toxic reactions not over 14.5 per cent. The toxic reactions other than agranulocytosis include leukopenia, drug fever, skin eruptions, lymphadenopathy, salivary adenopathies, and others. Some of them are distressing, but none alarming.

In our own clinic we have used the drug almost exclusively as a preparation for thyroidectomy, and have no experience on toxic side-effects when the drug is used over a long period as treatment per se.

In the matter of recurrence of thyrotoxicosis or relapse, Williams found in 100 cases treated with thiouracil for many months, that 49 stayed well

without treatment after discontinuation during periods of observation from 3 to 21 months. Fifty-one patients had relapses within 0.5 to 5 months, and in 66 per cent of these the relapse occurred within one month. Riker and Wescoe have this to say: "In the more than 1000 cases already reported, approximately 10 per cent continued satisfactorily after the drug was withdrawn. It is noteworthy that in one series of 48 patients in which a thyroid remission was induced by thiouracil therapy for six months or longer, the therapeutic effects continued in 77 per cent of the cases when the drug was withdrawn. There seems to be a relationship between the duration of therapy and the tendency to maintain a thyroid remission after therapy is discontinued. Astwood has advised at least six months of treatment." They further point out that it is important "that all patients who relapse can be retreated successfully with the drug." However, in this connection it should be pointed out that toxic reactions, as in the case of sulfa drugs, probably are more frequent in reëxhibitions of antithyroid drugs than in the original course, and one would not dare reëxhibit the drug in cases in which there had been any idiosyncratic toxic reaction with the first course, or reaction which involved the hematopoietic system.

What then can one say of the relative merits of surgery and of treatment with antithyroid drugs? Nothing with complete finality, of course, but we can weigh the pros and cons in each case. Astwood [15] has pointed out that mortality due to drug is no higher than that due to surgery at its best. In Moore's compilation, deaths due to drug amounted to 0.5 per cent of total treated cases. The operative mortality in skilled hands these days is in about the same neighborhood.

In favor of treatment by drug alone it might be said, therefore, that there is no greater risk, and the ordeal of a surgical operation (or operations) and the cost of hospitalization is avoided. The danger of death from operation, however, does not extend usually over more than 24 hours, whereas the danger of agranulocytosis due to drug, with possible death therefrom, continues as long as the drug is exhibited, perhaps for many months. From the point of view of psychic trauma, not only to the patient but to the doctor, these time relations weigh heavily in favor of an operative program. The long continued close observation of patients on drug therapy alone also imposes a heavy burden on patient and doctor, which is much greater than in surgical treated cases. Persistences and remissions following surgery, moreover, amount to not more than 5 per cent or less. Evidently they are much higher so far in the cases in which drug therapy alone is used.

In comparing surgical with drug therapy, one also must take into account the number of permanent tetanies and vocal cord palseys that follow operation, and any lasting or late deleterious effects of the drug. With regard to the latter it may be said that, except when agranulocytosis is fatal, all toxic drug effects clear up promptly when the drug is omitted. But hypersensitivity to a drug may persist, and there is some experimental evidence to suggest that antithyroid drugs may predispose to later carcinogenesis.

The incidence of tetanies and vocal cord paralyses, transient or permanent, in the hands of expert thyroid surgeons should not be much over 1 per cent each.

The production of myxedema by either method need not concern us. That due to drug clears up when the drug is stopped; that due to surgery can easily be controlled by thyroid. Better a post-operative myxedema than a post-operative persistent or recurrent thyrotoxicosis.

How one will add up these and other pros and cons, will be determined largely by the personal equation. At the moment and until there is more abundant late result data, I feel justified myself in still preferring the operative program to that of prolonged drug therapy. But I fully expect that drugs with less and less toxic effect will be developed, and that one day I might easily prefer drug treatment to operation.

In contrast to that on antithyroid drugs, the literature on the therapeutic use of radioactive iodine is as yet very scanty. The first publication on its use as a tracer in the study of thyroid physiology and as a possible therapeutic agent, that I can find, is that of Hertz, Roberts and Evans [16] in 1938.

The idea back of treatment of thyrotoxicosis by means of radio-iodine was, of course, that inasmuch as the thyroid gland collects iodine specifically, the giving of radioactive iodine would implant radiation directly within the cells which it was desired to irradiate, and that such treatment, therefore, might be more effective and less injurious to neighboring tissues than roentgen-rays administered from without.

Hertz and Roberts [17] presented in May 1942, a preliminary report on 10 cases of Graves' disease treated by radioactive iodine, and at the same meeting (American Society for Clinical Investigation) Hamilton and Laurence [18] reported on three. Hertz and Roberts [19] have just reported again on their series, which now numbers 29 cases. With doses of radio-iodine varying from 3 to 21 millicuries and followed by courses of ordinary iodine, they claim that 20 of the 29 patients were apparently well three years after treatment.

After Dr. Hertz joined the Navy in 1943, Drs. E. M. Chapman and R. D. Evans [20] studied and treated another series of cases using heavier dosage of radio-iodine, namely, from 15 to 79 millicuries, and no other therapy. Of 22 patients so treated, 20 appear well at the end of two years. The remaining two are improved but still have elevated metabolic rates. In two cases of the last mentioned series, biopsies performed after irradiation showed extensive fibrosis of the thyroid with small scattered islands of hyperplasia of thyroid parenchyma.

What then shall one say of this mode of treatment? Certainly it is *an* effective way of causing a remission (perhaps permanent) in the thyrotoxicosis of Graves' disease. That much can be stated definitely. Whether it is equal to, or better than, surgical ablation of the thyroid or treatment with antithyroid drugs cannot be said at the present time. The number of cases treated is as yet small, and none has gone over five years. It can be said

that to date there has been no mortality and as yet no evidence of toxic or untoward side-effects except occasional transient roentgen sickness in some of those patients receiving the heavier dosage.

The possibility of late carcinogenic action must not be lost sight of, and it should also be borne in mind that the radioactive iodine not held by the thyroid is excreted in the urine. In the process of excreting the radioactive element, the kidney may be subjected to a considerable amount of radiation which could conceivably damage it. The only evidence we have as yet on renal damage is in the case of one woman with a preceding low grade chronic pyelonephritis which became exacerbated transiently following the exhibition of radio-iodine.

As between programs of equal therapeutic merit, the choice should go to the one which costs the patient the least time, money and annoyance. It is quite possible that from these angles the choice will go to radio-iodine, but the question of relative therapeutic merit, as indicated before, cannot yet be determined.

Yet another non-surgical method of treating Graves' disease, but one which cannot be appraised at all because of paucity of data, is irradiation by roentgen-ray of the pituitary. There is literature on this method going back at least as far as the paper by Borak in 1935.[21] Until the brief report of W. O. and P. K. Thompson[22] in 1944, however, the experience has been largely in the use of the method to treat the ophthalmopathy rather than the thyrotoxicosis, and for that purpose the results have not been impressive. In seven of the 38 cases of the Thompsons, the metabolism dropped permanently to within normal limits. In 16 a temporary reduction in metabolism of from 15 to 52 points was observed. In 15 there was no change.

The rationale of the treatment, of course, is that subduing the pituitary in its thyrotropic activity may attack the disease at a more fundamental level than that of the thyroid.

It is conceivable that irradiation of the pituitary might directly affect the ophthalmopathy in a way treatment aimed at the thyroid would not. But my guess is that roentgen-ray treatment of the pituitary for either the thyrotoxicosis or the ophthalmopathy of Graves' disease will not survive in competition with other methods now available. There is always the danger that one may destroy some other function of the pituitary than the thyrotropic, which one is aiming at. I wrote Dr. E. Perry McCullagh[23] and asked whether any patients he had treated for exophthalmos by irradiation of the pituitary had shown subsequent evidence of hypopituitarism. He replied that in one such case definite anterior lobe hypofunction did develop.

Conclusions

1. The so-called antithyroid drugs when used in combination with iodine, in the preparation of patients with Graves' disease for thyroidectomy, pro-

vide a more complete preparation than has ever been available before.

2. As between treatment of Graves' disease by thyroidectomy after preparation with an antithyroid drug in combination with iodine, and treatment by prolonged use of an antithyroid drug alone, the author believes that the scales still tip in favor of surgery.

3. Treatment with radioactive iodine is *an* effective way of producing a remission in the thyrotoxicosis of Graves' disease, but any final evaluation of how it compares with other modes of treatment must await observation of more cases and over a longer period of time, particularly with respect to late untoward side-effects, malignancy, renal damage, or others.

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PENICILLIN THERAPY ALONE IN NEUROSYPHILIS: AN ANALYSIS OF CLINICAL RESULTS*

By GEORGE D. GAMMON, M.D., F.A.C.P., and JOHN H. STOKES, M.D., with the collaboration of HOWARD P. STEIGER, P.A. Surgeon (R), U.S.P.H.S., WILLARD H. STEELE, M.D., HERMAN BEERMAN, M.D., NORMAN R. INGRAHAM, JR., M.D., PAUL GYORGY, M.D., ELIZABETH ROSE, M.D., JOHN W. LENTZ, M.D., and with the assistance of ABRAHAM ORNSTEEN, M.D., F.A.C.P., and DONALD SCOTT, M.D.,
Philadelphia, Pennsylvania

WHEN we began the treatment of neurosyphilis with penicillin in November 1943, we determined to use penicillin alone without fever or arsenic or any other therapy which could influence the course of the disease. This seemed the obvious way to find out what the drug could accomplish, and we have followed this plan with a few exceptions which are noted. In substituting a new régime for the older routines of arsenicals and fever, we felt an urgent obligation to keep a close check on clinical effects as well as the results of blood and spinal fluid reactions. Furthermore, by carefully observing those manifestations of the disease which may be checked or reversed, we hoped to assess more rapidly the results of the new treatment. For these reasons, in this report we consider the effect of penicillin on the symptoms and signs and course of the disease in patients, all of whom were followed for over three months to two years (to November 15, 1945). The diagnostic categories and period of follow-up are listed in table 1.

All patients in the study were examined routinely, originally at one month, later two and, finally, at three month intervals. Although this follow-up program was not always realized, it came close to achievement, since 97 per cent of the cases were followed successfully. A complete neurologic examination was made at each visit, and symptoms were listed on a case card to insure uniformity of information.

As a method of evaluating results of treatment, patients were graded as to abnormality on a 1–4 basis. Following administration of penicillin, the case was graded for change of physical and mental status or lack thereof.

* Read at the Twenty-Seventh Annual Session, American College of Physicians, Philadelphia, May 13–17, 1946.

From the Institute for the Study of Venereal Disease, University of Pennsylvania and United States Public Health Service coöperating, and the Department of Neurology and the Penicillin-Syphilis Panel of the University Hospital. The Institute, the Departments of Neurology, Ophthalmology, Dermatology and Syphilology, and Pediatrics, and the Division of Venereal Disease Control, Philadelphia City Department of Public Health, and the Philadelphia General, Pennsylvania, and Children's Hospitals are represented in the authorship.

The work described in this paper was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Pennsylvania.

The investigation was assisted by contributions from the Gar Wood Research Fund and the Kirby-McCarthy Fund.

Improvement was expressed in grades 1–4 or "normal," showing the degree, if any, to which the course of the disease had been changed by treatment in the intervals between examinations. The gradation of "worse," 1–4 likewise, was employed, and "unchanged" described an unaltered mental and physical status following treatment. An evaluation of the case as a whole was made on the changes in individual symptoms and signs. For the purpose of reporting the result, grades of improvement were combined into classes "moderate" or "marked" improvement. The same type of grading was used for cases which became worse.

In addition to a full clinical examination, certain special tests were utilized in some cases: tests of visual fields and acuity, electrocardiograms, electroencephalograms, records of speech and of handwriting. Blood and spinal fluid were tested by a battery of technics. The methods employed in the use of penicillin in neurosyphilis by the Penicillin in Syphilis Group of

TABLE I
Follow-Up, Months

Cases		24 to 18	18 to 12	12 to 6	6 to 4
Total	161	33	34	57	37
Paresis	19	5	3	7	4
Tabo-paresis	28	6	2	11	9
Juvenile Paresis	10	1	2	3	4
Tabes	54	8	17	19	10
Meningo-Vascular	31	9	8	9	5
Asymptomatic	19	4	2	8	5

the University of Pennsylvania have been in part outlined in a previous paper,[1] and only essential additional items are here included.

Dosage and Administration of Penicillin. Sodium penicillin in aqueous solution was given intramuscularly every four hours at the beginning of the study. Later, the drug was administered routinely every three hours for a period of eight days until dosage totalled 1.2 to 2.4 million Oxford units. Since May 1945, a new system of dosage, in which the unit is 4.8 million units, has been employed. This is given in three ways: as a single course within eight days; as a single course within 16 days; and as two courses of 2.4 million units each within eight days, the courses being administered seven months apart. In addition to this standard therapy program, there were exceptional instances in which a higher dosage of over 4.8 million units was employed. A few received three courses.

Results. In all the types of neurosyphilis treated with penicillin, the outstanding therapeutic response was a gain in weight which continued for

several months following treatment. This increase amounted to from three to 50 pounds, the majority of patients gaining 15 to 20 pounds, apparently owing to a better appetite and added ingestion of food. A sense of well-being usually accompanied this gain. It is almost as though check was given the infection to which Moxon referred in his aphorism, "Syphilis is a fever diluted by time."

Paresis and Tabo-Paresis

In order to compare our results with those of others, it is necessary to emphasize the fact that we were dealing with patients who could be cared for in a general hospital without locked wards. Our cases could be classed in three categories: (1) those with early and mild symptoms of mental derangement who could still do unskilled work; (2) cases with mild residual symptoms in spite of extensive treatment, including fever; (3) cases with severe

Table II

Paresis and Tabo-Paresis

Result	Overall Effect				Mental State			
	Par.	Tabo-Par.	Total	%	Par.	Tabo-Par.	Total	%
Improved	14	21	35	74	14	20	34	72
Markedly	6	11	17	36	6	13	19	38
Moderately	8	10	18	38	8	7	15	32
Unchanged	2	5	7	15	2	6	8	18
Worse	2	0	2	4	2	0	2	4
Death	1	2	3	6	1	2	3	6
Total	19	28	47		19	28	47	

paretic mental breaks of short duration. Thus, of 47 paretics and tabo-paretics, 38 per cent had symptoms for one year or less, and 57 per cent for two years or less. Twenty-six were unable to work because of mental symptoms. Eight had had fever therapy, all except two, two years or more before penicillin treatment.

Considering the results as a whole, table 2 indicates that approximately three-fourths of the cases improved and in 38 per cent this improvement was marked. Fifteen per cent were unchanged, 4 per cent became worse, and 6 per cent died, a total of 25 per cent unimproved. Fever was given shortly after the penicillin treatment to two of the three who died, without influencing the course of the disease.

Mental symptoms improved in 72 per cent of the cases, but 18 per cent were unchanged and 4 per cent became worse; 28 per cent therefore were

unimproved mentally, three of whom were institutionalized. Of the 26 unable to work because of mental changes rather than because of locomotor causes, 17 were able to return to work after treatment.

The most arresting result was observed in the paretics with severe mental break of short duration. The first change, often beginning toward the end of treatment, consisted of an improvement in coördination and tremors. This progress was demonstrated by better speech and handwriting and later by gait. Decrease in tremor occurred in all cases and in about three-fourths tremor disappeared completely. Toward the end of treatment or shortly

TABLE III

Paresis and Tabo-Paresis Cases Unable to Work Because of Mental Changes

Able to go back to work	17
Unable to work before or after	6
Died	3
TOTAL	26

afterward, mental improvement began and continued thereafter for some months. The confusion and disorientation commenced to clear, memory improved, delusions began to yield, and hallucinations to disappear. Within three to four weeks after treatment, these gains were obvious to all. The appetite improved and weight was added. These phases of progress continued for the next three to six months after a single course of treatment.

In the cases with less severe mental changes, less obvious and slower results were noted. In the first year following treatment, the patients gained more insight, became calmer, and the ability to hold a job returned.

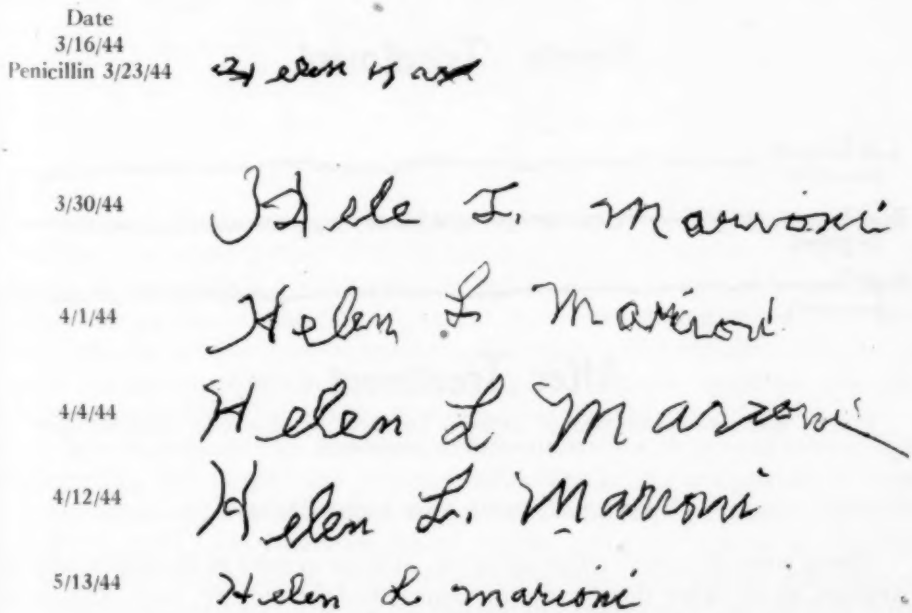

FIG. 1. Signatures of a tabo-paretic treated with penicillin.

Reflex activity showed much less alteration. In five cases the increased tendon reflexes became somewhat less active and in two instances a positive Babinski sign disappeared. But in 34 cases, hyperactivity of tendon jerks continued. Pupillary abnormalities were unaffected.

In 19 patients there were electroencephalographic changes. In some the abnormality consisted of slow waves of 2 to 3 per second. In others an activity of 5 to 7 per second was of particular interest, for during or following treatment this 5 to 7 per second activity tended to speed up toward the normal alpha pattern of 9 to 11 per second. Of the 19 cases cited, 16 were reëxamined and 12 showed improvement following therapy. The evidence furnished by this objective test clearly indicates that an alteration of cortical activity may be observed following penicillin therapy. A more detailed report with Dr. Donald Scott is being made elsewhere.

Taking these results as a whole, in this type of neurosyphilis there is clear-cut evidence that penicillin has an active therapeutic effect.

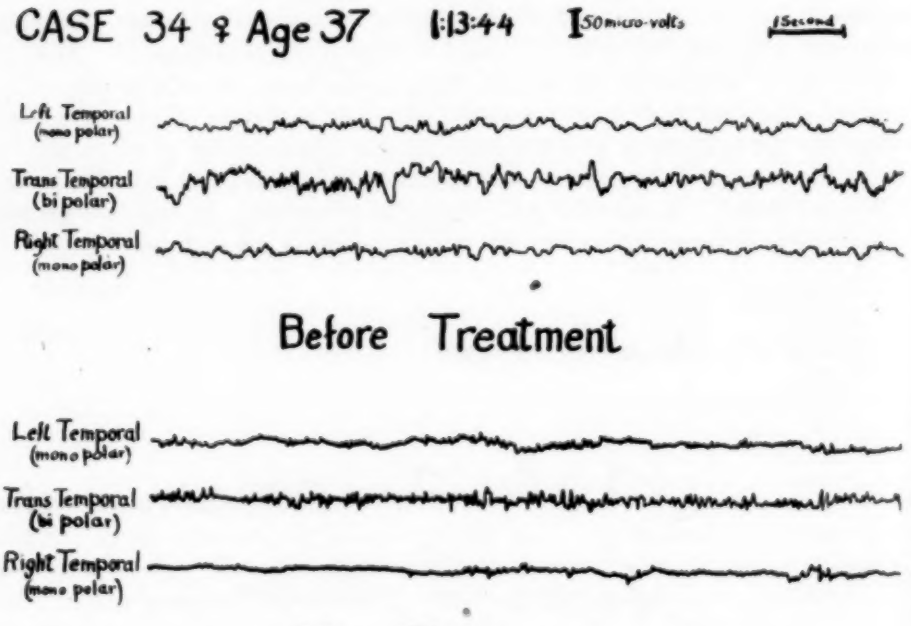

FIG. 2. Electroencephalogram of paresis. Decrease in slow-wave activity after treatment with penicillin.

JUVENILE PARESIS AND TABO-PARESIS

There were 10 cases in this category, and the results of penicillin administration, as of other therapeutic measures used heretofore, were less satisfactory than in acquired paresis and tabo-paresis.

The overall evaluation in five juvenile paretics and tabo-paretics remained unchanged under penicillin therapy; one patient became worse. In this patient, who was observed carefully over a long period of time with frequent psychological tests and under instruction in the Psychology Department of the University, there was slow deterioration which was not arrested by fever therapy employed after penicillin proved inadequate (table 4).

Four of these juvenile cases improved moderately in their general condition and mental status. Station and gait in the congenital syphilitic patients were unaffected by penicillin therapy except in one instance, and tremors were unaltered. Speech was moderately improved in one instance and deteriorated in another. The drug had no effect upon sensory abnormalities or the condition of the pupils. A definitive evaluation of treatment in this type of patient, particularly in comparison with other methods, cannot be made at this time, but the results do not suggest that penicillin has solved this most difficult problem of neurosyphilis.

TABLE IV
Juvenile Paresis and Tabo-Paresis

	Overall Effect	Mental State
Improved Moderately	4	4
Markedly	0	0
Unchanged	5	4
Worse	1	2
Death	0	0
TOTAL	10	10

TABES

In the complex symptomatology of tabes, there can be seen a mixture of mechanisms representing both destruction and stimulation. Pain is the result of stimulation and should respond promptly to any effectual therapy which stops the stimulation. Ataxia, incontinence, impotence and reflex loss are the evidence of destructive processes which advance slowly. On these latter symptoms, effectual therapy can become apparent only if it checks the progress, and this requires a time-scale of years.

We chose for study, therefore, chiefly tabetics with typical tabetic lightning pain, and despite the obvious difficulties in an analysis of this subjective symptom, we believe that our observations are, in the main, authentic. Patients were questioned in detail on the duration, character, location, severity and frequency of pains before treatment. Following penicillin administration, each was given a mimeographed sheet on which he kept a pain

calendar with details of location and severity and medication required for relief. Most of the patients conscientiously kept the data, and from the charts and the frequent interviews, we assembled the data on which we base these statements.

The survey showed that (table 5) in the 55 tabetic and tabo-paretic patients, there were 40 who had lightning pains before treatment. There was some degree of improvement in 82 per cent following penicillin therapy regardless of the number of courses administered. In 15 per cent pain disappeared completely, and in approximately one-third of the cases the improvement was marked, while in another one-third it was of moderate degree. The pains were unchanged in 12 per cent and became worse in 17 per cent of patients. Of 15 patients in whom no pain had been present, four developed pain during or after administration of penicillin, a Herxheimer-like reaction which sometimes was seen in the use of penicillin. Ten patients

TABLE V

Tabes and Tabo-Paresis with Pain

Pain Before Treatment		Pain After Treatment						
		Improvement				No Improvement		
		None	Marked	Moderate	Total	Unchanged	Worse	Total
Moderate	24	6	4	9	19	3	2	5
Severe	16	0	9	5	14	2	0	2
TOTAL	40	6	13	14	33	5	2	7
Per cent		15	32.5	35	82	12.5	5	17.5
No Pain	15					11	4	
TOTAL	55							

had recurrence of pain following temporary relief from the first course of treatment. These were retreated on the basis of pain. Four of these had two or more relapses. The duration of pain did not appear to influence its response. There was no significant difference in the results of treatment in cases in which the tabetic pain had been present more than or less than five years.

In view of the occasional Herxheimer exaggeration of pain and of the more frequent relief of pain, it appears to us that penicillin is acting on the process responsible for the pain. The effects are greater than might be expected as a result of spontaneous remission, and on the whole compare well with results of other forms of therapy.

In three cases with gastric crises, definite improvement was noted in two and slight improvement in another. These cases required large amounts

of penicillin and were retreated if the pain recurred. One man received intraspinal therapy. It is much too early to know if these effects will prove permanent. Brief abstracts of these cases follow:

One patient (CM) suffered so severely from pain that he developed suicidal tendencies. However, immediately after the first treatment with penicillin, the gastric pain subsided. There remained only a mild prickling pain in the epigastrium occurring at approximately three day intervals and lasting for about 25 minutes. On two occasions this was associated with nausea. Codeine controlled this type of pain whereas the earlier pain had responded to morphine only. This patient is greatly improved.

In a second case (CT) prior to therapy the pain had recurred every three weeks. Following total dosage of 10 million units, 340,000 units of which were given intrathecally, the intervals between the crises became longer, and although there is some question of psychic overlay in this patient, he insists he is improved by treatment and appears to be improved.

TABLE VI

Gastric Crises in Tabes; End Result

Case	Yrs.	Pain	Vomit	Length	Frequency	Dose	Follow-up (Mo.)
CMA	3	Severe; slight	Severe; none	2–3 days 2 hours	Weekly; 6 mo.	10	15
EB	¾	Mild; none	Mild; none	1–2 wks. none	Monthly; none	13.6	12
CT	3	Severe; less	Severe; less	3 weeks 1 week	3 weeks 6 weeks	10	10

The first line describes conditions before treatment; the second line after treatment.

In case 3 (EB) there had been a great deal of treatment, including Swift-Ellis and fever therapy, prior to penicillin administration. These proved ineffectual. Six months after the initial administration of 1.2 million units of penicillin, the attacks of vomiting, which had previously occurred every two or three weeks, ceased. However, after 13.6 million units of penicillin, the daily nausea persisted in this patient although her general condition improved.

In the remaining symptoms of tabes, no very striking changes were noted, and when the patients claimed some improvement, it was usually of a nature and degree which was more obvious to them than to the examiner. Ataxic gait is an illustration; in only two cases could definite improvement be seen although 12 more claimed they walked better. Seven patients considered themselves worse.

Impotence, partial or complete, was present in 19 and six of this number claimed some improvement in function. No deterioration of normal function occurred. Urinary incontinence, partial or complete, was present in 13,

five of whom thought they had better control after treatment. In 33 without previous evidence of bladder difficulty, five developed some disability following therapy, and in four of these this was clear evidence of an unfavorable course of the disease.

Pupillary abnormalities were unaffected and absent reflexes were unchanged. No patient lost reflexes or developed pupillary changes while under observation.

In some cases a complex mixture of improvement and progression could be seen. In the cases in which pain improved, ataxic gait became worse in six, improved in three, and remained unchanged in one. One patient improved in sexual ability but became worse in gait, bladder and mental functions. In four cases, improvement occurred in gait, bladder and potency, but lightning pains, absent before treatment, developed. These mixed responses increase the difficulty in assessing the value of therapy and emphasize

TABLE VII

Tabes Dorsalis

Symptoms and Signs		Abnormal before Treatment			Normal before Treatment	
		Better	Same	Worse	Worse	Same
Ataxia	33	18	12	4	3	21
Impotence	19	6	13	None	None	35
Urinary Incontinence	18	5	8	0	5	28
Pupils Abnormal		None	All	None	None	All
Reflexes		None	All	None	None	All

the view expressed above that a long period of observation is necessary. Apart from the effect on pain, then, in tabes very little improvement has been seen. One has the impression that these cases lack the elasticity of response seen in early paretic cases.

SPINAL SYPHILIS

This type of syphilis, which is sometimes combined with tabes, is the result of vascular disease of the cord at one or more levels. Fluctuation in signs may be abrupt and there is a special hazard of transverse myelitis if treatment is too enthusiastic. Fortunately, some cases declare themselves beforehand by girdle pains on the trunk, sensory impairment to the level of the pain, and positive Babinski signs in the lower extremities; with this may go the absent reflexes and posterior column signs of tabes. One patient of this kind (DB) developed a transverse myelitis in the first 36 hours of treatment, became weak in the legs, but in the end improved until he was better off

than before. Another case went steadily downward despite treatment. Low initial dosage of penicillin should be given to these cases.

Meningo-Vascular Syphilis

The yardstick for therapy in this group is the spinal fluid and blood response. Clinical evaluation rests on whether the disease gradually progresses. Of the 31 cases, three died, one in the Hospital and another at home unobserved. A third was killed in an accident. One case originally diagnosed meningo-vascular became frankly paretic. Three other cases may have had a progression of the disease, but the diagnosis was based on findings which are not conclusive. In one patient (WL) pupil reactions were less prompt; in another (DB) loss of deep pain in the Achilles tendon developed in the 18 months of observation; in a third (AH) vibratory sensation became slightly impaired. In four cases, then, the disease obviously became worse.

Table VIII

Spinal Fluid under Penicillin

(Results in Per cent)

Type		Grades 3, 4 N and NN	Normal NN	Worse
Paresis	16	62	31	
Tabo-Paresis	37	58	39	
Meningo-Vascular	33	73	45	
Tabes	51	86	57	4
Congenital	16	81	63	
Asymptomatic	30	70	60	

Grades 3 and 4 mean improvement in three or four of the following components of the spinal fluid: cells, protein, Kolmer test or colloidal mastic.

NN (near normal) signifies spinal fluid with cell count 5–10, protein 20–40, negative Kolmer test, and colloidal mastic 1111000000.

Little comment is required concerning recovery from strokes affecting various parts of the brain. In eight cases the recovery differed in no way from the behavior of nonsyphilitic cases. Headaches were greatly reduced following penicillin therapy.

Convulsions. Seizures occurred in two meningo-vascular cases, five paretics, four tabo-paretics, one tabetic, and two congenital paretics, a total of 14 cases. Two of these patients had partial continual epilepsy which was undoubtedly the result of cerebral hemorrhage, for hemiplegic signs developed as well as homonymous field cuts and sensory loss, and the spinal fluid became xanthochromic. In one of these, the signs developed in the first 24 hours of treatment, in the other just before treatment. The latter

was treated with penicillin alone, and the twitching slowly subsided in 36 hours, probably without relation to this therapy. Anticonvulsants have been necessary to control both of these cases, and in the whole group there is only one case which has not required anticonvulsant medication. Penicillin therefore will not prevent these seizures.

Asymptomatic Cases. In the period of observation, one patient of the 21 developed pupillary abnormalities. The others remained without signs or complaint.

Dosage

Recent studies on the composition of penicillin have divided it into several fractions called G, F, K and X. Of these, K is less effective in syphilis than the other fractions. Throughout the period covered by this investigation, the relative percentage of these fractions has changed, but in unknown

Table IX

Effect of Dosage (Million Units) on Overall Evaluation in Paresis and Tabo-Paresis

		1.2	2.4	4.8	2.4+2.4	1.2+2.4 or 2.4+1.2	Multiple High
Improved	35	3	7	8	3	5	9
Total Unimproved	12	1	5	1	2	1	2
Unchanged	7	1	1	1	2	—	2
Worse	2*	—	2	—	—	—	—
Died	3	—	2	—	—	1	—

* One case 3.0.

Multiple high includes doses above 4.8 and up to 10 million. (Some cases given 3 courses of treatment.)

amounts. Today's penicillin has more K and is therefore less effectual in syphilis than the 1943 vintage. Relapse rates in early syphilis reflect this.

This fact, unfortunately, vitiates any analysis of dosage effects. Furthermore, no valid data on dosage can be obtained until we have an unvarying compound. Fortunately, as the study progressed we gave larger doses, partly because we had more drug available, and this may have offset the declining antisyphilitic properties.

Neither the spinal fluid findings nor our data on clinical results in paresis and tabo-paresis showed any significant difference between the single course of 1.2, 2.4 or 4.8 million, nor between any of these and multiple courses, nor between low (to 4.8) or higher (above 4.8) dosage.

An analysis of dosage in relation to the effect on tabetic pain reveals only that the patients with most severe pain received the largest amounts of penicillin in repeated courses until some measure of relief was secured. Larger

doses were required here than in other cases, often from 6 up to 12 million units.

Despite current uncertainties, this can be said. If the patient can be kept under close and continuous observation, it is safe to give initial doses of 2.4 or 4.8 million units. If paretics with mental breaks fail to improve in four to six weeks, more penicillin, or fever should be given. In less urgent cases, retreatment should be given in four to seven months if the response has been inadequate. Tabetic pains may require higher doses, up to 12.0 million units and multiple courses.

Decision to retreat was made on the basis of these factors: failure of spinal fluid to become normal; failure of reversible symptoms to respond; relapse in spinal fluid; relapse or progression in symptoms.

Clinical and spinal fluid checks should be made at three month intervals during the first year and six month intervals thereafter.

Neural Herxheimer Reactions. During the first 24 to 36 hours of treatment, some patients showed an exaggeration of neural signs or symptoms. Quite frequently in paretic cases a mild increase in mental abnormalities was seen. Severe and dangerous reactions occurred in six cases. One nearly died in convulsions (CF), one bled into his brain and developed partial continual epilepsy, and two others had milder seizures. One of these (HM) also became confused and agitated and had hallucinations for the first time. All of these four patients, however, ultimately became very much better. Another paretic (SA), however, became maniacal and ultimately died.

Two cases developed transverse myelitis but ultimately recovered and even improved. Reference to one of these cases (DB) has been made above. Increase in tabetic pains occurred in four cases; in one, in each of two courses of treatment (JA).

To offset these reactions we cut the original four to six doses to 6,250 or 12,500 units and since then have had only one reaction which developed during retreatment. If a severe reaction occurs, treatment should be interrupted for one to two days and resumed at low dosage level. Special care is required in spinal syphilis.

From these experiences, it is clear that penicillin can be a dangerous drug and must be used with caution.

Fever, when it occurred, was not over 100° or 101° F. and lasted 12 to 24 hours. It has been too slight to have influenced the disease.

Differential Diagnosis

As with Medicine, syphilis is the tutor of Neurology. In examining some 300 neurosyphilitics, difficult problems in differential diagnosis inevitably arise. These fall into three classes: (1) the type of neurosyphilis, (2) syphilis combined with other disease, and (3) syphilis versus other disease, including reaction to penicillin. In regard to the first category, one cannot but be impressed with Wilson's dictum that neurosyphilis is pathologically

one and indivisible. The diagnoses herein made are based on the chief clinical features of the case.

In the second category, errors can only be avoided by constantly raising the question: Is any other disease present? Failure to do so led to missing an angle tumor in an old tabetic. The early papilledema was attributed to syphilitic neuritis. A spinal cord tumor was diagnosed in a syphilitic from the clue of yellow spinal fluid. This had been observed repeatedly over several years without comment. Especially difficult is the differentiation of non-syphilitic psychoses in syphilitic patients, particularly an evaluation of the nature of arteriosclerotic brain disease in a syphilitic.

In the third category are a group of cases without syphilis which show positive spinal fluid reactions. The blood reactions are negative and the patient has never had antisyphilitic treatment. We have seen this in the presence of a spinal cord tumor in three cases. In all of these spinal fluid protein was high. We have also encountered it in other diseases of the nervous system including acute multiple sclerosis. In one case of this kind, spinal fluid tests gave a biologically false-positive reaction. In another case with hemiplegia, the reaction cleared up at the end of treatment. The nature of these reactions is not clear but the important point is that they occur in nonsyphilitic patients. Further study of these will be made.

Spinal Fluid and Blood

The observations on spinal fluid and blood in this material, and a few additional cases, have been analyzed in a recent paper by John H. Stokes, et al., and only the salient points will be noted here.

Successive evaluations in May and October, 1944, and November, 1945, have shown that an increasing number of fluids became normal:

	Grade of improvement	
	3 and 4	Normal NN
May, '44	56	2.6
October, '44	33	26.0
November, '45	18	62.0

A previous analysis in terms of dosage and numbers of courses had demonstrated a trend toward better results with higher doses than lower doses and better results with two courses than one course. In the present material, however, this trend was not apparent. Tables 10 and 11 emphasize the similarity of effect of one course and of doses below and above 4.8 million units. Further study will be necessary to obtain conclusive evidence on these points. The factors which we know modify the result are the length of follow-up and the type of case, as well as total dosage and the time over which it is given. Our present routine of a standard of 4.8 million units.

described above, may provide adequate evidence when sufficient follow-up time permits analysis.

The results for various types of cases are seen in table 8. Asymptomatic and congenital cases gave the best response and paretics the least response.

The time course of change in the spinal fluid is of interest. Cells and protein dropped quickly and mastic and Kolmer tests followed. The major part of the change occurred in the first four months, but with longer observa-

TABLE X

Spinal Fluid Response in Relation to Dosage and Period of Observation*
A Comparison of Low and High Dosage

Amount of Treatment		*Low Dosage* 1.2 to Less than 4.8 Million in 1 or 2 Courses; 92 Cases		*High Dosage* 4.8 to 10 Million and over in 1 to 4 Courses; 83 Cases	
Observation 120–364 Days	Slight Imprvt.	10		7	
	Marked Imprvt.	10	Strikingly improved 35 cases 69 per cent	14	Strikingly improved 37 cases 71 per cent
	NN and Normal	25		23	
	No Change	3		5	
	Worse	3		3	
Observation 365–599 Days	Slight Imprvt.	3		6	
	Marked Imprvt.	4	Strikingly improved 24 cases 84 per cent	6	Strikingly improved 14 cases 67 per cent
	NN and Normal	20		8	
	No Change	2		1	
	Worse	0		0	
Observation 600 Days and Over	Slight Imprvt.	1		1	
	Marked Imprvt.	1	Strikingly improved 10 cases 84 per cent	2	Strikingly improved 9 cases 90 per cent
	NN and Normal	9		7	
	No Change	1		0	
	Worse	0		0	
Remarks		75 per cent strikingly improved		72 per cent strikingly improved	

* This includes all neurosyphilis, a total of 175 cases with abnormal spinal fluids.

TABLE XI

Spinal Fluid Response to Penicillin in Relation to Number of Courses*
By Period of Observation and Irrespective of Dosage

Number of Courses		1—81 Cases		2—75 Cases		3—16 Cases	
Observation 120–364 Days	Slight Imprvt.	7		9		1	
	Marked Imprvt.	13	Striking imprvt. 47 cases 78 per cent	8	Striking imprvt. 22 cases 60 per cent	2	Striking imprvt. 2 cases out of 3
	NN and Normal	34		14		0	
	No Change	2		5		0	
	Worse	5		1		0	
Observation 365–599 Days	Slight Imprvt.	1		6		1	
	Marked Imprvt.	4	Striking imprvt. 14 cases 88 per cent	4	Striking imprvt. 19 cases 70 per cent	2	Striking imprvt. 5 cases out of 6
	NN and Normal	10		15		3	
	No Change	1		2		0	
	Worse	0		0		0	
Observation 600 Days and Over	Slight Imprvt.	0		1		1	
	Marked Imprvt.	0	Striking imprvt. 4 cases 100 per cent	2	Striking imprvt. 9 cases 82 per cent	2	Striking imprvt. 6 cases out of 7
	NN and Normal	4		7		4	
	No Change	0		1		0	
	Worse	0		0		0	
Remarks		80 per cent striking improvement		67 per cent striking improvement		81 per cent striking improvement	

* 3 cases given 4 courses (1 slightly improved, 1 no change, 1 normal), making the case total of 175, were not included, as numerically insignificant.

tion it is apparent that the improvement continued over several months in some cases.

There was less response in blood than in spinal fluid and there was no recognized correlation between them. Only 30 per cent of cases with initially sero-positive bloods improved in those in which the spinal fluids became normal (82) or were markedly improved (115). The proportion of

serologic failure, despite marked spinal fluid improvement, was about 46 per cent. The blood findings had little significance for symptomatic or spinal fluid results.

A comparison of the results of malaria and other forms with penicillin therapy must eventually be made. With only two years of penicillin treatment, it is obvious that no final conclusions can be drawn. The results of the Coöperative Clinical Group were compared with our penicillin results and are taken from the article by Stokes et al. in the *Journal of the American Medical Association*. Results of penicillin on spinal fluid were better than malaria or chemotherapy in asymptomatic neurosyphilis and were of the same order of magnitude in the other types. Clinical results to date do not yet

TABLE XII

Comparison of Reported Coöperative Clinical Group Results with University of Pennsylvania Penicillin Results

Spinal Fluid Reduced to Normal (Results in Percentages)

	Tabes	Dementia Paralytica with Tabes	Dementia Paralytica	Meningo-Vascular	Asymptomatic
Routine	29	17	11	43	36 (1 yr.)
Swift-Ellis	49	28	18	59	39.2 (1 yr.)
Tryparsamide	40	46*	17	47	15 (1 yr.)
Malaria	22	12	9	0*	1.2 (1 yr.)
Penicillin†					
Normal	33	30	0	30	53
Near Normal	24	15	31	15	7
TOTAL	57	45	31	45	60

* Less than 20 cases.
† Fifty-eight per cent of these cases observed 1 year or less, 29 per cent up to 600 days.

equal those of malaria, but with lengthening experience, it seems probable that penicillin results will approach those of older routines. At the present time we consider it a safe first therapy.

SUMMARY AND CONCLUSIONS

1. One hundred sixty-one cases of neurosyphilis were treated with penicillin alone from November 1943, to July 1945. The results, as measured clinically and by blood and spinal fluid change, showed that penicillin is an active therapeutic agent.

2. The greatest effect on symptoms and signs occurred in the mental breaks, the incoördination, tremors and speech defects of paresis and in the lightning pains of tabes. Fixed pupils, absent reflexes and other signs of destructive lesions did not improve.

3. Spinal fluid abnormalities were particularly responsive to penicillin. The effect on asymptomatic cases was greatest and on paretics least. Blood responses are less than spinal fluid responses.

4. Penicillin is the first choice for the first treatment of neurosyphilis. This statement may be qualified for severe paretics. In these, failure to improve promptly indicates further treatment, either more penicillin or fever. Dose schedules are discussed in the light of the various factors involved including the changing character of penicillin. Adequate clinical and spinal fluid follow-up is essential.

Case Reports

RR, white male, 52 years of age; paresis with marked clinical and serological improvement.

This patient, in 1943, developed attacks of epigastric pain and paresthesias of the ankles. He was unable to work because of progressive forgetfulness and tremors of the hands.

On February 10, 1944, neurological examination showed unequal pupils which reacted sluggishly to light, grossly slurred speech and tremors of the face. Coördination of both upper and lower extremities was greatly impaired, especially on the right side.

On February 24, 1944, treatment with penicillin was begun and a total of 2.4 million units was given within an eight day period, without untoward reaction.

On March 22, 1944, the patient was reëxamined and his mental state proved to be one of mild euphoria, but station and gait appeared to be normal. The Romberg test was negative. There was slightly impaired coördination of both extremities and a tremor of the left upper extremity when the hands were extended. Tendon reflexes were equal and slightly increased. Sensations of touch, pain, position and vibration were normal. There was no change in the pupils. There was tremor of the right side of the face and definite slurring of speech. The patient was not able to work.

Reëxaminations were made at approximately two month intervals throughout 1944 and 1945 and on October 31, 1945 the patient was found to be mentally clear, with a negative Romberg. His coördination and reflexes were normal. He had no epigastric pain and the paresthesia of the ankles had been relieved. There remained a slight tremor of the lips and tongue.

The most recent examination, February 20, 1946, revealed a return to a practically normal physical and mental status except for the inequality of the pupils. However, vision, too, had improved, and the patient had returned to work. The original spinal fluid report showed: Wassermann 4444; protein 75; mastic 4555543110, while the test of October 31, 1945, showed Wassermann 0000; protein 20; no cells; mastic 1111000000.

It need not be emphasized that in this case both the serological and clinical remission was of marked degree.

HM, female, white, married, 47 years of age; taboparesis. Symptoms increased during treatment but ultimately improved.

In February 1944, this patient developed severe mental changes with delusions of paranoid trend. There was disability of gait so marked as to cause falls on several occasions. In one fall the patient broke several ribs. There was dribbling from the bladder.

The past history of the patient is irrelevant except that between the ages of 20 and 29 she had had epileptic seizures with unconsciousness and tongue biting.

Neurological examination showed considerable weakness of the lower extremities with bilateral absence of the patellar and Achilles tendon reflexes. Biceps and triceps reflexes were normal. The fundus of the eye could not be seen owing to opacities in the lens. The right pupil was larger than the left but both pupils reacted sluggishly to light and accommodation. Extraocular movements were normal. There was no facial weakness, but a tremor of the lips was present and the tongue protruded in the midline with marked gross tremors.

On March 23, 1944, the patient was given penicillin therapy, a total of 4 million units. On the ninth day of treatment she developed an attack of unconsciousness lasting for a few minutes. This, apparently, was a Herxheimer reaction to the drug.

At the end of treatment, although still ataxic, the patient was able to get up and walk about. However, during treatment the mental condition deteriorated and she developed auditory delusions with confusion.

Reëxaminations were made at intervals in 1944 and 1945 and it was decided to repeat the penicillin dosage. September 17, 1945, 4.8 million units were administered. The improvement in gait and other physical and mental symptoms continued at slightly accelerated pace. On examination August 22, 1945, the gait had become almost normal, the mental and physical status had improved markedly. The reflexes were practically normal. There was almost no slurring of speech with test phrases. Her handwriting had improved markedly. The original spinal fluid showed: Wassermann 4444; protein 47 and a mastic 443221000 while that of April 17, 1945 showed: Wassermann 0112; one cell; protein 20; and mastic 2221100000.

CF, female, white, married, 37 years of age; paresis. Severe convulsions during treatment. Marked improvement later.

In November 1943, the husband noticed personality and behavior changes in this patient who became careless in her dress and of seclusive habit.

A year earlier she had been struck by a trolley and hospitalized for severe contusions and lacerations on the right side of the head in the region of the frontal bones. She was discharged later from the hospital in normal condition. The original diagnosis was multiple cerebral concussions.

After her return home she developed auditory hallucinations and was confused. She was again hospitalized January 7, 1944. She was conscious and coöperative but showed a loss of recent and remote memory and Romberg test was negative. Coordination of the upper and lower extremities was normal except for a minimal tremor of the hands. The tendon reflexes were somewhat diminished, the triceps increased. The patellar and Achilles reflexes were markedly exaggerated. There was no ankle or patellar clonus. Sensation of touch, pain, heat, and temperature was normal.

The pupils were equal and regular and reacted to light and convergence. There was a fine tremor of the upper lip. There was tremor of the tongue and greatly impaired speech.

On January 19, 1944, penicillin was administered, and after receiving 23,000 units, the patient developed a series of right-sided convulsive attacks involving the face, and, at times, the arms and legs. She appeared to be aphasic. There was a bilateral Babinski sign and slight facial weakness.

Penicillin was discontinued and the attacks were controlled with oxygen. The patient appeared to be extremely ill during the following 24 hours. The blood pressure fell to 80 mm. Hg systolic and 40 mm. diastolic, she became cyanotic and there was twitching of the right upper extremity.

Within two days, however, the condition cleared and there was no weakness of upper or lower extremities or face. The Babinski sign had disappeared. Penicillin was administered again and she was given 1.2 million units without further untoward reaction.

The ultimate reaction to the drug was dramatic. Tremors of the extremities diminished, and the hallucinations disappeared. Memory, apparently, was completely restored. The only remaining symptoms were slight tremors of the facial muscles, the tongue and upper extremities.

By October 11, 1944, the patient had gained 27 pounds and was practically in normal mental and physical condition.

Another examination on January 23, 1946, showed continued improvement. The patient was able to hop on either foot; coördination and reflexes were normal. The pupils reacted equally to light and convergence. The only complaint was continued slight tremor of the facial muscles.

JA, white, female, 36 years of age; tabes. Lightning pains brought on by treatment on two occasions.

In October 1943, this patient developed paresthesias of the third and fourth fingers of the right hand. The toes of the left foot became somewhat stiff and numb.

Neurological examination at admission January 1944, showed the pupils were equal and reacted to light and convergence. There was a slightly positive Romberg test. Tests of coördination and strength were normal. There was no definite impairment of sensation, vibration, touch or position. There was generalized hyporeflexia. Biceps reflexes were greatly diminished, the triceps less so. The abdominal reflexes were present. No patellar or Achilles jerks were obtained. There was a negative Babinski response.

This patient received 1,200,000 units of penicillin within eight days. After the fourth injection, hives appeared over all the body. Treatment was suspended temporarily and the hives subsided.

At the end of treatment, shooting pains of tabetic type and short, stinging pains affected the region of the right shoulder, the upper extremities, calf of the leg and anterior surface of the thigh. There was cramping of the tendons of toes, in the left calf and posterior thigh muscles. These pains subsided in approximately three weeks.

The paresthesia of the toes and the headaches disappeared following therapy.

On examination one month later, February 16, 1944, there was no essential change in the patient's symptoms except increased sensation in the toes, and a second course of 2.4 million units of penicillin was administered. Pains recurred during the second course of treatment and there was very slight residual cramping of the fingers.

On October 10, 1945, the patient stated the lightning pains were less severe and less frequent. There was still a slightly positive Romberg and the right fourth finger was still painful. Otherwise, the patient was in excellent condition.

There was no recurrence of the hives or the lightning pains.

DB, white, male, married, 38 years of age; Herxheimer effect; transverse myelitis with recovery.

This patient was in good health until the summer of 1942 when he developed numbness and paresthesia of the medial aspect of the thighs and genitalia. His local physician gave him a course of 58 injections, apparently with little effect. Seven months later deep, sharp pains of the lower extremities appeared, which came on in bouts and lasted two to three hours. More recently there was also diplopia.

Neurological examination revealed an ataxic gait, a positive Romberg, absent knee and ankle jerks and impairment of pain, temperature and vibration sense as far as the iliac crest. There was also ptosis of the left lid, sixth nerve weakness and sluggish pupils. There was tremor of the tongue and the speech was slurred.

The skull plate was negative and the visual fields were normal while the diplopia fields revealed a right rectus palsy. The blood and spinal fluid serologic reactions were positive with a paretic colloidal mastic curve. The electroencephalogram showed no significant abnormalities.

On January 24, 1944, the patient was placed on penicillin, 25,000 units every four hours. On January 27, 1944, the man complained of considerable pain and increased weakness of the legs. Patches of dermatitis appeared on the right lower leg, and macular eczema on the extensor surfaces of the arm and buttocks. There was a positive Babinski response in the lower left extremity when the patient was lying down but not when sitting up.

Although the original neurological findings indicated a diffuse and patchy meningo-vascular syphilis with considerable posterior column involvement and a typical paretic cerebrospinal fluid, the greatly accentuated symptoms following therapy seemed to be the expression of a Herxheimer-like reaction.

Penicillin was discontinued to be resumed February 2, 1944, the 25,000 units being reduced to 12,500 units for two doses after which the 25,000 unit dosage again was administered until 1,200,000 units of the drug had been given without further untoward reaction.

The patient was examined thereafter at frequent intervals and found to be slowly improving clinically and serologically. The tabetic pains still were frequent although less severe in character and another course of 2.4 units of penicillin was given December 11, 1944. There was no Herxheimer effect during retreatment.

The most recent examination, November 14, 1945, showed there was less pain and less weakness in the limbs. There was still a positive Romberg. The mental condition was clear; sensation was normal and there were no tremors.

The spinal fluid findings of February 2, 1946, showed no cells, a negative Wassermann, protein 10 milligrams, and mastic of 1110000000.

HH, male, colored, married, 38 years of age; paresis. Subarachnoid hemorrhage during treatment. Subsequent improvement.

In 1940 this patient went to Pennsylvania Hospital because of convulsions. A diagnosis of paresis was made and the patient given 54 hours of fever therapy. Tryparsamide was also administered.

In 1944 the patient returned to Pennsylvania Hospital because of attacks of vomiting without diarrhea. The serologic reaction was positive at this time. The history showed that in 1943 the patient had developed a shuffling gait, that he stumbled easily and that the convulsive seizures still were present. About April 1944, marked mental changes with hallucinations and delusions developed, and the patient became incontinent. His local physician had him admitted to Philadelphia Psychiatric Hospital where he was given 12 injections of typhoid vaccine. His response was unfavorable and at the request of his physician on June 1, 1944 he was admitted to the Hospital of the University of Pennsylvania where the original neurological examination showed him to be definitely psychotic.

On June 19, 1944, penicillin was started and two days later a generalized convulsion occurred. This heralded a subarachnoid hemorrhage and a left hemiparesis. Therapy was interrupted a few days and then resumed for a total dosage of 2.4 million units.

Neurological examinations at frequent intervals thereafter revealed steady improvement in his physical and mental condition except that occasional convulsions still occurred. On January 15, 1945, 1.2 million units of penicillin were administered.

No convulsive seizure or other type of Herxheimer reaction followed this therapy and all examinations since have showed the patient's steady improvement.

On examination February 6, 1945, the man was greatly improved, although not normal, mentally and physically, and the Romberg sign was negative. He has now returned to work. Residual signs of his disease were slight tremor of the tongue and of the left facial muscles. However, anticonvulsant medication was necessary to control his seizures.

The results which have been presented in this paper must be interpreted in light of the fact that from June, 1943, the date of inception of the study, to the present, commercial penicillin has been a changing mixture of various substances. The content of "impurities" has gradually decreased as potency, in terms of units per mg., has increased. The relative amounts of the several identified penicillin fractions G, F, X, and K have likewise varied from time to time. Those two changes, and perhaps others, suggest that therapeutic efficacy may not have remained constant; and that it may be significantly different today from what it was originally. It is now impossible to assess the extent to which these changes may have affected the results here reported.

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AN EVALUATION OF SULFONAMIDE MIXTURES AND VARIOUS ADJUVANTS FOR CONTROL OF SULFONAMIDE CRYSTALLURIA *

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RENAL complications due to sulfonamide therapy continue to be among the most frequent and serious attending the use of these drugs.[1, 2, 3] Two main causes are established: (1) irritation due to formation in the kidneys or ureters of crystals largely of the acetylated drug and (2) nephrotoxic action. The causes of the latter are poorly understood. However, there is ample evidence to show that crystalluria is the result of the very low solubility of the acetylated drugs in urine that is acid in reaction.[4, 5, 6, 7, 8] Despite numerous demonstrations of the effectiveness of alkalinization [6, 9, 10, 11, 12] by means of sodium bicarbonate, lactate or citrate, many physicians either fail to employ alkalinization as a means of diminishing renal toxicity or use inadequate amounts to accomplish this result. Although the belief is widely held that administration of enough fluid to insure high urinary output is sufficient to overcome this hazard, our experience like that of others [13] indicates that high urine volumes alone will not forestall sulfonamide precipitation, and that crystalluria is frequently observed in patients secreting large volumes of urine. If the hazard from this source is to be held to a minimum, additional measures are required.

A study of various means of decreasing or preventing renal irritation by sulfonamide crystals has been conducted coincidentally with other investigations of various sulfonamides in the Medical Wards of the Philadelphia General Hospital.† The study has included trial of sodium bicarbonate at several dosage levels. Additional information has been obtained concerning the critical pH of urine at which crystal-containing urines are divided from crystal-free urines and of the quantity of alkalinizing agent required to exceed the critical pH. We have had in mind also the fact that administering sodium salts in the required quantity has certain disadvantages and have studied the use of potassium bicarbonate, urea, ammonium chloride and sodium chloride for their effects on crystalluria.

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From the Committee on Chemotherapy and the Division of Biochemistry, Philadelphia General Hospital.

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A new approach to the problem has been offered by the work of Lehr [14, 15] who proposed the use of mixtures of sulfonamides as a means of increasing total solubilities. He found that aqueous solutions saturated with sulfadiazine would dissolve appreciable additional quantities of another poorly soluble sulfonamide such as sulfathiazole or sulfamerazine. Thus if sulfadiazine and sulfamerazine are administered as mixtures containing equal parts of these drugs, the total amount of each excreted in the urine will be decreased and the concentrations in urine lowered, with diminished likelihood of crystal formation. A preliminary report on the behavior of sulfadiazine-sulfamerazine mixtures * with respect to crystal formation in urine is included in this paper.

Plan of the Investigation

For the study of adjuvant drugs patients were assigned to the various treatment groups by a procedure designed to assure random selection. The cause of illness was pneumococcic pneumonia in about three-fourths and meningococcic meningitis in the remainder of the total number of patients. Our interest during the greater part of this study was mainly in sulfamerazine, and most of the patients studied, therefore, received this compound. The remainder received sulfadiazine or a mixture of sulfadiazine and sulfamerazine. Patients received 4 to 6 grams of drug daily. Further information concerning procedures used may be found in recent publications by the authors from this hospital. Alkalies or other agents intended to influence crystal formation were administered at the same time as the sulfonamides. All patients received sufficient fluid to maintain urinary output at the highest levels possible. An output of 3000 ml. was sought but in some seriously ill or markedly dehydrated patients this was not achieved.

The presence of crystals of acetylated sulfonamide derivatives in urine offers a practical indication of the solubility of these derivatives in the urine and of the potential hazard from intra-tubular or intra-ureteral concrement formation. Urine samples were collected between 7 a.m. and 2 p.m. An entire voiding was transferred to bottles and kept at 38° C. until examined. This was usually within an hour, although occasionally longer. Comparison of the specimens so collected with others examined immediately after being collected from the same patient showed close agreement with respect to occurrence of crystals, although an increase in count of crystals did occur in some specimens. Aliquots of 50 ml. were centrifuged, the sediment was suspended in 0.5 ml. of urine, and portions were examined in a counting chamber under the microscope. Counts were made of the number of crystals and red blood cells present. "Crystals" refers to the characteristic acetylated sulfonamide forms. Presence of crystals other than those of sulfonamides was disregarded. When the identity of the crystalline material present was uncertain, a portion of the sediment was washed and analyzed chemically.

* Sulfadiazine-sulfamerazine mixtures used in our studies were supplied as "Combisul-DM" by Dr. Norman L. Heminway, Schering Corporation, Bloomfield, New Jersey.

pH was determined by means of a glass electrode. Loss of carbon dioxide from the urine could not be prevented, and the measured pH thus was more alkaline than the actual pH of the urine in the bladder.

Red blood cells were so commonly detected by microscopic examination of urine from patients suffering from pneumonia or meningitis, both in the presence or absence of renal irritation by the sulfonamide administered, that their utility for detection of untoward effects of the sulfonamide was quite limited.

Results

The incidence of sulfonamide crystals in urine in sulfadiazine treated patients of the control group was the same as that observed in patients receiving sulfamerazine under similar conditions (table 1).

Table I

Frequency of Crystalluria Due to Sulfonamides as Influenced by Various Agents Relationship to Urine pH

Drug	Adjuvant		Crystalluria		Per cent	Urine pH		
	Type	Dose	Present	Absent				
		gm./day	Number of Specimens			Av.	Low	High
Sulfamerazine	None		41	114	26%	5.98	4.95	8.70
Sulfadiazine	None		17	46	28%	5.88		
Sulfamerazine	Sodium bicarbonate	6	14	45	24%	6.27	5.04	8.88
Sulfamerazine	Sodium bicarbonate	12	9	146	6%	7.14	5.16	9.23
Sulfamerazine	Sodium bicarbonate	24	3	97	3%	7.62	5.54	8.70
Sulfamerazine	Potassium bicarbonate	7.5	12	33	27%	5.98	5.08	7.55
Sulfamerazine	Potassium bicarbonate	15	10	32	24%	6.56	5.00	8.74
Sulfamerazine	Ammonium chloride	4	14	37	27%	5.59	4.87	7.33
Sulfadiazine	Sodium chloride	24	4	15	21%	5.71	4.98	7.13
Sulfamerazine	Urea	10	5	25	17%	5.93	5.02	8.60
Sulfadiazine	Urea	10	0	16	0%	6.08	5.44	7.04
Sulfadiazine-Sulfamerazine mixture	None		10	163	6%	—	—	—

When the urine pH was less than 7.15, about one specimen in four contained crystals of acetyl sulfamerazine (figure 1). When the pH was greater than 7.15, only one of 220 samples showed crystals of acetyl sulfamerazine. In this exceptional sample the pH was 7.57. Below pH 7.15, there was no correlation between pH and incidence or number of crystals per specimen.

Comparison of the groups receiving 6, 12, and 24 grams of sodium bicarbonate daily (table 1) shows that the incidence of crystalluria was unchanged from that of the control group when only 6 grams were administered. Twelve grams of sodium bicarbonate lowered the incidence of crystalluria to 6 per cent, as compared with a 23 per cent incidence in the group

receiving 6 grams. Twenty-four grams of sodium bicarbonate daily lowered the incidence of crystalluria to 3 per cent. This is not significantly different from the response of the 12 gram group when tested by the Chi square method, but the number of crystals per specimen was considerably lower when the higher dose was used.

The effect of the different dosages of sodium bicarbonate on urine pH is shown in figure 2 and explains clearly the ineffectiveness of the 6 gram doses.

Potassium bicarbonate was ineffective in both 7.5 and 15 gram dosages in reducing the incidence or number of crystals in urine (table 1). Figure 3 shows that potassium bicarbonate caused relatively little change in the urine pH; far less than that brought about by sodium bicarbonate in equivalent

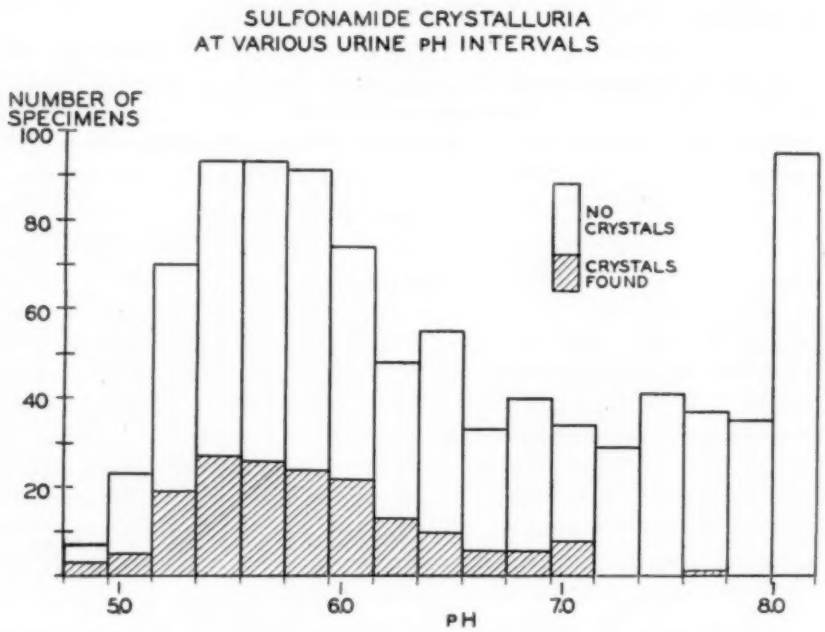

FIG. 1. Sulfonamide crystalluria at various urine pH intervals.

concentrations. Higher dosages of potassium salts were purposely avoided because of possible potassium retention with rise in concentration to levels causing depression of cardiac function in patients suffering from severe infections.

Ammonium chloride was used to learn whether further acidification of the urine would increase the frequency of crystalluria. However, the proportion of urines showing crystals was no greater than that of the patients of the control groups (table 1, figure 3).

Urea offers possibilities as an adjuvant to sulfonamide therapy, because of its action as a diuretic and because the solubility of the sulfonamides and of their acetyl derivatives is greater in urea solutions than in water.[16, 17]

Table 1 shows that there is a somewhat lower incidence of crystal-containing urines in the urea treated group. Figure 3 shows that this effect was not due to change in urine pH. The number of individuals who could be studied was too small to permit conclusions to be made concerning its effectiveness.

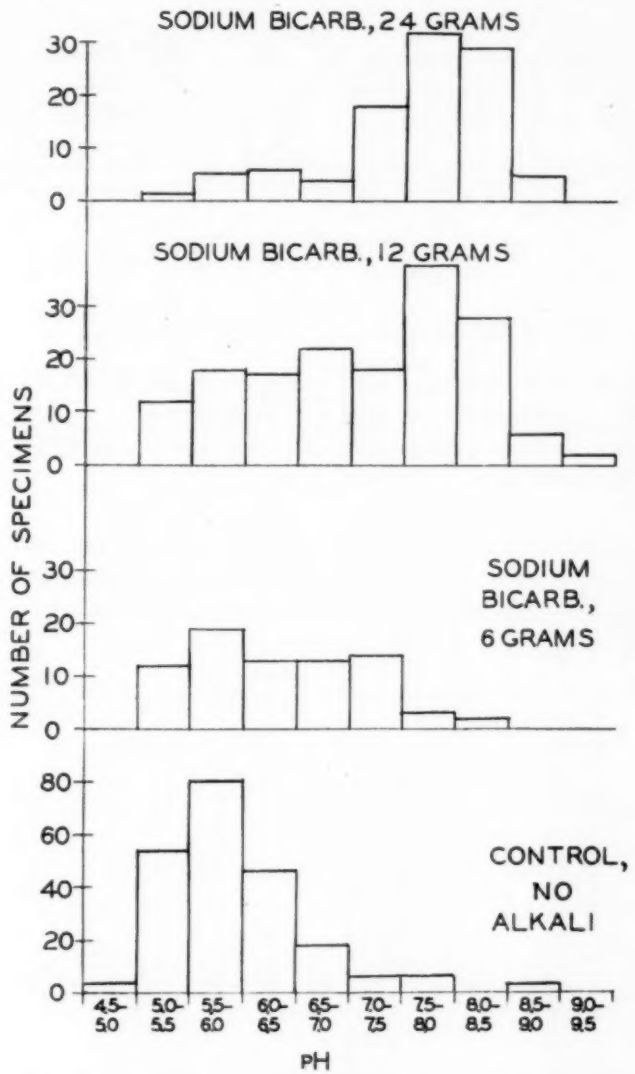

FIG. 2. Effect of sodium bicarbonate at several dosage levels on urine pH.

Further trial of urea is warranted, particularly since its use involves fewer hazards than does that of sodium or potassium salts.

The use of sodium chloride was suggested by the report of Lehr [18] who found it to be effective in treatment of urinary tract complications due to

sulfonamides. Although the number of subjects here also is too small to permit conclusive evaluation, the incidence of crystal-containing urines appears to be unaltered (table 1).

The effect of sodium bicarbonate administration on concentration of sulfa-

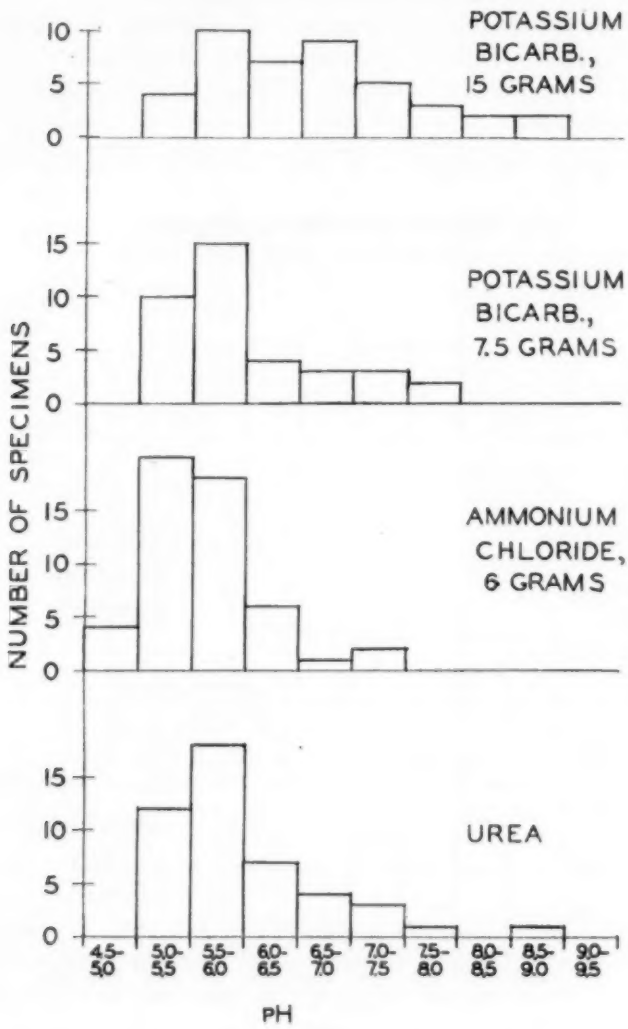

FIG. 3. Effect of potassium bicarbonate, ammonium chloride and urea on urine pH.

merazine in blood plasma is shown in table 2. Six grams of sodium bicarbonate daily is without effect, but 12 and 24 grams cause sufficient increase in excretion to lower the plasma concentration to an extent that is statistically and perhaps therapeutically significant.

TABLE II

Effect of Administration of Sodium or Potassium Bicarbonates on Concentration of Sulfamerazine in Plasma

Alkali	Dose	Number of Samples	Sulfamerazine Average Concentration
	gm./day		mg./100 c.c. plasma
None		70	13.4 ± 6.9
Sodium bicarbonate	6	59	13.2 ± 7.7
Sodium bicarbonate	12	73	11.5 ± 6.5*
Sodium bicarbonate	24	112	10.6 ± 4.9**
Potassium bicarbonate	7.5	65	12.1 ± 5.2
Potassium bicarbonate	15	59	12.9 ± 5.9

* Statistically significant difference.
** Highly significant difference.

COMBINED SULFONAMIDE THERAPY

Administration of sulfadiazine and sulfamerazine in mixtures containing equal parts of the two compounds resulted in a substantial decrease in the frequency with which crystals were found in urine compared with either drug alone (table 1). The total amount of drug given was the same, and concentrations in serum were comparable. Crystals were found in 6 per cent of the urine specimens when the sulfadiazine-sulfamerazine mixture was administered at the rate of four to six grams daily. The patients in this treatment group received no alkali or other adjuvant. Thus it may be seen that the

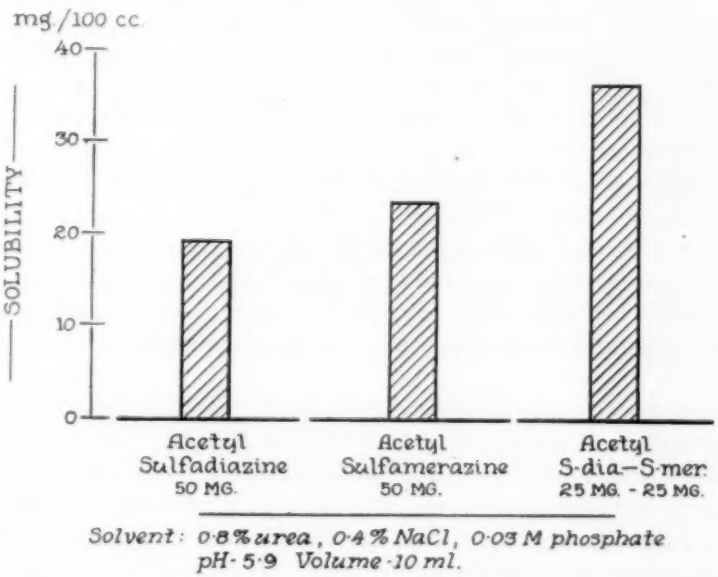

FIG. 4. Solubility of acetyl sulfadiazine and acetyl sulfamerazine singly and in mixtures.

incidence of crystals is the same as that in patients receiving either sulfadiazine or sulfamerazine alone when 12 grams of sodium bicarbonate were administered daily. However, a single patient of the 54 patients that have received sulfonamide mixtures showed gross hematuria associated with sulfonamide crystalluria. The therapeutic response to such a mixture in patients suffering from pneumococcic pneumonia and bacterial meningitis was satisfactory and will be the subject of a separate report.

Lehr's work on solubilities of sulfonamides in mixtures did not include studies of the acetylated derivatives. Since it is the latter that constitute the hazard of concrement formation, it seemed important to establish whether they would conform in their behavior to that of the sulfonamides themselves. Experiments devised for this purpose have shown that this is true and that the acetylated compounds also give higher total solubilities in mixtures (figure 4).

Discussion

Formation of crystals and concretions of acetylated sulfadiazine and closely related sulfonamides is known to depend mainly upon (1) the concentration of the compound, (2) whether it is present in the form of acid or salt, and (3) concentration of urea and other constituents of urine having a solvent action. It is clear that the volume of urine secreted will determine (1) and (3) to a large extent and will also influence (2). Low volumes of urine will lead to high concentrations of the acetylated sulfonamides. At the same time proportionately less urea and other solvent substance will be present in the urine, since the acetylated sulfonamides are secreted by the tubules [19] while the urea and associated substances are passively or actively reabsorbed. Concentrated urine also is more acid. The desirability of maintaining high urine outputs is acknowledged by all who have investigated the problem of sulfonamide concretions, yet it is at times difficult to maintain adequate urine volumes in seriously ill and febrile patients. Also, deposits of crystals may occur despite relatively high volumes of urine. Additional precautions thus are required. The solubility of the acetylated sulfonamides can be markedly increased by converting them to sodium salts. This conversion becomes appreciable at pH 7.0 and rises with great rapidity as the reaction becomes more alkaline. Concomitantly, crystals of these compounds disappear from the urine and the frequency of renal irritation decreases.

An alternative method, proposed by Lehr [14, 15] avoids exceeding the critical concentrations at which crystallization will occur by using two or more sulfonamides simultaneously. Our preliminary observations indicate that this approach is as effective as the administration of sodium bicarbonate at the rate of 12 grams per day. The use of sulfonamide mixtures avoids certain disadvantages associated with the administration of sodium bicarbonate, namely the retention of sodium with or without alkalosis, and the lowering

of plasma concentrations of the sulfonamide consequent to administration of effective amounts of sodium bicarbonate.

Urea, investigated because of its combined action as diuretic and solvent, also offers promise. Again its use is especially advantageous when sodium salts should be avoided.

Potassium salts have been advocated [20, 21] for use in such patients, but our data show them to be far less effective than sodium salts in equivalent amounts.

Summary

1. The incidence of characteristic crystals of acetyl sulfonamide in urine was the same when patients received either sulfadiazine or sulfamerazine.

2. The critical pH of urine dividing crystal-containing from crystal-free samples was pH 7.15. Below pH 7.15, change in pH had no influence on occurrence of crystals.

3. Comparison of various amounts of sodium bicarbonate administered with the sulfonamide shows that at least 12 grams daily was required to lower the incidence of crystals substantially. Raising the bicarbonate intake to 24 grams daily was of doubtful benefit when all factors were considered.

4. Potassium bicarbonate was relatively ineffective when compared with sodium salts.

5. The response to urea as an adjuvant indicates that while less effective than sodium bicarbonate, its use may be beneficial.

6. A saturated solution of acetyl sulfadiazine will dissolve appreciable amounts of acetyl sulfamerazine. Thus the solubility of such a mixture is additive and exceeds that of either compound measured singly.

7. The use of sulfadiazine and sulfamerazine in mixtures containing equal parts of each drug led to a markedly decreased incidence of crystalluria compared with that observed when either compound was administered singly.

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IMMUNIZATION AGAINST INFLUENZA *

By Jonas E. Salk, M.D., and Thomas Francis, Jr., M.D.,
Ann Arbor, Michigan

Despite the fact that the greatest advances in knowledge of human influenza have been made since 1933, the name "influenza" invariably conjures up thoughts of 1918. Since the influenza viruses were not discovered [1, 2, 3] until more than a decade later, there can be no certainty regarding the relationship between the viruses known today and the 1918 episode. Nevertheless, it seems probable that the influenza viruses will be found to be causally related to future recurrences of the highly fatal disease. In comparing the pandemic of 1918 with subsequent epidemics, Francis [4] has remarked: "The differences enumerated appear to be those of degree—quantitative differences of broad epidemiologic rather than specific clinical or etiologic nature."

Epidemiologic Variations

For centuries pandemics of high mortality have constituted a recurrent threat to each generation. However, it should be emphasized that epidemics of a much milder disease are almost yearly occurrences. The epidemics of mild disease, known to be caused by Types A and B influenza virus, are characterized chiefly by a high degree of morbidity, but there also occurs a significant but variable increase in mortality. Since the discovery of the virus, epidemics of influenza A have occurred every two to three years, and it appears that the cycle for influenza B may be four to six years. Epidemics studied in the past 13 years have been due to one or the other of these viruses, but some year the independent cycles may coincide, resulting in a mixed epidemic. Simultaneous or successive infections by the A and B viruses in the same individual would, under these conditions, be possible. The consequences cannot be foreseen, since widespread occurrence of disease resulting from a combined infection by both viruses, or from a second attack by the virus of one type during the convalescent phase of infection by the other, is unknown, although occasional instances have been reported.

Apart from the widespread epidemics which call attention to the problem, it is now known that the disease occurs in localized outbreaks at times when generalized prevalence is not evident. Moreover, there have been repeated demonstrations of sporadic or isolated cases in the intervals between epidemics. Epidemiologically, then, influenza resembles other epidemic dis-

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eases in which man is the reservoir and in which the host-parasite relationship is in constant fluctuation.

Clinical Variations

Correlated clinical and laboratory investigations have revealed that wide variations exist in the clinical picture of influenza virus infections. As is the case with other recurrent infectious diseases for which immunity is short-lived, the clinical manifestations in the adult are modified by the residual immunity from previous exposures, while in children a more uniform picture is presented. Reference to a particular study [5] illustrates this point in a young adult population. During the epidemic of influenza A in November and December 1943, observations were made in a group of approximately 900 unvaccinated men. In this group only 8 per cent were hospitalized with what might be called "typical" influenza. The criteria for hospitalization were based upon Army regulations requiring admission to hospital with temperatures of 100° F. or more recorded by mouth. By "typical" influenza is implied a temporarily incapacitating illness with abrupt onset, associated with fever, generalized aching and symptoms of respiratory tract irritation. An additional feature is the absence of gross evidence of pathologic lesions characteristic of infection by other etiologic agents. Although only 8 per cent exhibited illnesses of this degree, serologic study revealed that 40 per cent of individuals had been infected in the course of the epidemic. Further review indicated that in addition to the 8 per cent who were known to have had influenza A, 17 per cent experienced what would ordinarily be included under the nondescript terms of "a bad cold," "URI," or, to use the Army terminology, "mild nasopharyngitis," and the remaining 15 per cent appear to have had asymptomatic infections caused by the virus of influenza A.

In addition to being the cause of a mild disease, it is recognized too that the viruses of influenza A and B are sometimes associated with severe, fulminating disease reminiscent of the 1918 variety. Although a tendency has prevailed in some quarters to reserve the diagnosis of influenza for cases of this kind, it would appear from the illustration cited that it is in error to use the severe clinical types as the point of reference in considering the possibility of influenza as an etiologic diagnosis. These brief remarks are intended to indicate that the viruses of influenza, against which an immunizing agent is desired, contribute to the incidence of respiratory disease of man to a wider extent and with greater clinical variation than is generally recognized.

These comments serve to indicate the nature and the extent of the clinical as well as the epidemiologic problems which influenza presents.

Immunization Against the Epidemic Disease

It would not be possible in a paper of this kind to refer to all of the work on influenza that contributed to the advance of the problem to its present state. Many fundamental investigations, which should not pass unrecog-

nized, were made in the interval between the early and the recent studies on immunization against the epidemic disease. In the final analysis, the fundamental contributions were essential prerequisites for success.

Very early in the research on human influenza, an approach to the solution of the problem of control by methods of immunization was indicated. That a rise in antibody titer occurs following natural infection was demonstrated. It was soon discovered that similar changes could be induced artificially by subcutaneous injections of active or inactive virus, without the production of disease. A variety of vaccine preparations was conceived, employing virus contained in the lungs of ferrets or mice, in tissue culture, in the developing chick, and finally in the allantoic fluid of the embryo. With more information regarding the virus itself and with greater understanding of the quantitative relationship between virus dosage and immunizing effects knowledge was advanced. The desirability for extending to man the experimental observations made in animals was apparent. The use of human volunteers as a guide for the study of vaccinating procedures, the effectiveness of different preparations, and the practicability of different approaches furnished important preliminary information without awaiting the occurrence of natural epidemics.

Activities were accelerated by the War. Many investigators collaborated in their efforts under the Commission on Influenza of the Army Epidemiological Board to show that a practical means could be devised for controlling epidemics of influenza. The development of the vaccination studies of the Influenza Commission has been reviewed.[6] A vast amount of information, both fundamental and applied, was obtained. The present discussion, however, will be limited to three practical questions: (1) the nature of influenza virus vaccines; (2) the degree of immunity engendered; and (3) the duration of immunity.

Nature of Influenza Virus Vaccines. The vaccine employed in the trials to be discussed consisted of a suspension of formalin-inactivated influenza viruses and contained representative strains of both types A and B. The culture medium for the virus was the chick embryo and the extra-embryonic fluids constituted the immediate source. Although these fluids are rich in virus, further concentration was deemed advisable in order to obviate the possibility of any failure that might be due to the use of insufficient antigen. Even though the precise dosage required was unknown, by concentrating the antigen it was hoped to compensate for the loss in immunizing potency for animals that accompanies virus inactivation. Two methods were devised for getting into a 1 ml. volume the quantity of virus contained in 10 ml. of extra-embryonic fluids of the developing chick. One method of concentration involves the collection of the precipitate formed when frozen allantoic fluid is allowed to thaw, and then resuspension of this precipitate, to which the virus is adherent, in one-tenth the original volume of the same fluid.[7, 8] In the other method the virus is permitted to be adsorbed on the red cells of the embryo from which it is then released by a change in temperature into a volume of

physiological salt solution equivalent to one-tenth the original volume of harvested fluid.[9] In the early studies of 1942–1943, vaccine prepared by both methods was employed. In the trials of vaccine by the Influenza Commission during the influenza A epidemic in 1943–1944, vaccine prepared by the red cell adsorption-elution method was used.

In these investigations a single injection of 1 ml. was given. A second inoculation seems to afford no further benefit in terms of antibody level. The booster effect noted with other immunizing agents is not observed with influenza virus. The side effects or reactions accompanying the use of influenza vaccine will be mentioned later.

Degree of Immunity. During the epidemic of influenza A that occurred throughout the United States in the winter of 1943–1944, 12,500 ASTP students were involved in studies conducted uniformly but independently by members of the Commission on Influenza in six investigating groups in different parts of the country.[10] In each study,[6, 11-15, 5] alternate individuals in a company received the virus vaccine, or were given a control inoculation. The accumulated statistics [10] indicated that 7.1 per cent of unvaccinated and 2.2 per cent of vaccinated individuals were hospitalized with "typical" influenza. Expressed in another way, 3.2 times as many control persons became ill as did those vaccinated; or 76 per cent of all cases occurred in that 50 per cent of the population that was unvaccinated. A further statement describing the result has been that a 75 per cent reduction in attack rate occurred, or that the vaccine was only 75 per cent effective.[16] Although at first glance this may seem to be a fair statement of the efficacy of vaccination, there are certain essential factors that require consideration for a critical evaluation of these data.[5] It is important to point out that in a study of the prophylactic effect of a vaccine against an epidemic disease that is transmitted from man to man, special consideration must be given to the controls for the following reasons. If the untreated individuals are interspersed with vaccinated persons in the same population and if the vaccine has any effect, the controls are no longer untreated since their opportunity for exposure necessary to contract disease is reduced, to say nothing of the quantitative aspects of exposure which probably determine severity. Thus, under such circumstances, the controls are not true controls since they are at a reduced risk when compared with the population at large. If, on the other hand, two populations are compared, one vaccinated and the other unvaccinated, the latter could then be considered a truly untreated group. However, there might then be some doubt as to whether chance played a rôle, or whether the epidemic would have struck with equal force if vaccination had not been done.

To return, then, to the estimate that vaccination was 75 per cent effective, this seems to assume that the attack rate in the control half of the populations under study was not influenced by the presence of vaccinated persons, but was the expected rate had vaccination not been done. Two observations which have a bearing on this point suggest that the assumption may be incorrect. (1) At the University of Minnesota [11] the attack rate among 1206 individuals

in the study group, half of which had received influenza vaccine, was 5.9 per cent. This rate was "considerably lower than in certain other groups on the campus, in one of which an attack rate of 38 per cent was observed among approximately 500 men, who were living under conditions similar to those of the vaccinated groups." (2) At the University of Michigan,[5] where the over-all incidence was 5.4 per cent in the study group, again one-half of which was vaccinated, an incidence of 20 per cent was observed in a company of unvaccinated men. These data are more to the point when it is recognized that in the two institutions the incidence of disease in the unvaccinated controls was 9.06 per cent and 8.58 per cent, respectively, as compared with the 38 per cent and 20 per cent in other comparable units in which no vaccination had been done. These observations strongly suggest that the incidence of illness recorded in the controls was influenced by the presence of an equal number of vaccinated persons and that the effectiveness of vaccination probably greatly exceeds that described by a comparison of vaccinated and controls in this study.

Certain of the investigators [14] have suggested that an epidemic involving a higher attack rate would discriminate less between vaccinated and control populations than does a disease of low rate, and that vaccination would be less effective if incidence rates were 20 to 30 per cent. Again, this assumes that the 7 per cent attack rate represents the true rate without influence of vaccination. That this assumption is open to question has just been indicated. In direct refutation, however, is the situation observed at the University of Michigan [5] where in the analysis of results a division was made in terms of residence, since it appeared that a much higher attack rate was observed in one group as compared with another. The higher rates were observed in those companies quartered in a large dormitory, while a much lower incidence occurred in a group of similar size dispersed in 11 fraternity houses. In the dormitory group of 824 men, an incidence of 13.39 per cent was observed in the unvaccinated half of the population as compared to 2.66 per cent in the vaccinated; whereas in the companies comprising 607 men in the 11 fraternity houses, the incidence in the controls was 4.65 as compared with 1.31 in those vaccinated. Contrary to speculations cited earlier, it would appear that a higher attack rate would enhance rather than diminish the difference between vaccinated and controls by affecting a relatively greater proportion of unvaccinated than vaccinated persons. A similar conclusion is suggested by an analysis of the antibody levels in vaccinated versus unvaccinated groups, in relation to the apparent reduction in susceptibility in individuals with higher antibody titers.[5]

Earlier in this paper mention was made of the fact that in the course of an epidemic of influenza the infections were manifested clinically in various forms, from the asymptomatic variety to the moderately severe disease. In the discussion thus far, incidence of disease, or attack rates, have expressed the amount of hospitalized illness arbitrarily called "typical" influenza. This is not a good term, but it expresses the idea. In the study at the University

of Michigan, all cases of respiratory disease occurring among the ASTP students were considered, including those cases that ordinarily do not come to the attention of physicians in private practice. It was of considerable interest that in this group of cases, the majority of which were afebrile or had oral temperatures of less than 100°, there was no difference in incidence between controls and vaccinated when a diagnosis of "localized infection of the respiratory tract" or "common cold" was made. However, when the diagnosis was "mild" influenza, a distinct difference between controls and vaccinated was evident, although the difference was much less than observed in terms of the more severe illness similarly diagnosed. Serological study showed that about 90 per cent of cases hospitalized because of severity were influenza A, while in the dispensary group about 65 per cent were caused by the type A virus. Inclusion of non-influenza cases in the latter category would tend to reduce the difference between controls and vaccinated; however, it is also believed that in many instances vaccination simply reduced the severity of illness and some who might have had "typical" influenza developed the milder disease that did not result in incapacitation.

Duration of Immunity Following Vaccination. The general opinion has been that the duration of effectiveness of influenza vaccination is rather short. It has been variously stated as being a matter of weeks or months. By and large such statements have been based on questionable evidence or have been made without due consideration of all of the factors involved. From recently reported studies, both *indirect* and *direct* evidence is available to support the contention that the duration of effectiveness of influenza vaccination is considerably longer than a few months, when vaccine of suitable potency is employed.

The *indirect* evidence is as follows: From studies conducted by Hirst, Plummer and Friedewald [14] in New York and Hale and McKee [12] in Iowa during the epidemic of influenza A in 1943–1944, it was learned that prior to the seventh day following inoculation, no difference in incidence of illness occurred in vaccinated and control subjects. Thus, it seems that approximately a week is required for the development of the immunizing effect. This phenomenon appears to coincide with the development of a demonstrable increase in specific antibody in the serum. It might be expected, therefore, that the degree of persistence of the increased antibody titer resulting from vaccination might reflect the duration of immunity, just as the appearance of serum antibody parallels the onset of immunity. This possibility becomes more plausible when it is considered that in a comparison of vaccinated and unvaccinated individuals who had corresponding levels of serum antibody, the probability of contracting influenza was of the same order.[5] It should be borne in mind that the antibody titers in the unvaccinated subjects must represent the residual effect from a previous natural exposure which occurred, very probably, not more recently than three years before. The apparent identity in significance between antibody produced by natural infection and antibody stimulated artificially by vaccination strengthens the hypothesis

that the measure of persistence of the increased antibody titer following vaccination may indicate the degree of persistence of immunity.

With this in mind let us examine the information available on the question of the rate of decline in antibody titers elevated by vaccination. Studies were undertaken during the winter of 1942–1943 [17] to test the efficacy of vaccination, using the same vaccine preparation referred to earlier; that is, one in which virus was concentrated approximately ten-fold by adsorption from the allantoic fluid onto the red cells of the embryo and subsequent elution. The anticipated epidemic did not occur until a year later. In the interim, however, antibody titers were determined in vaccinated persons at intervals up to the onset of the epidemic one year after vaccination. The findings were rather surprising in view of previous reports that the increased antibody titer following vaccination was fleeting and that the duration of immunity was brief. With respect to the serologic results, they revealed that mean antibody titers declined gradually from the two-week maximum, but were still well above the prevaccination level at the end of 12 months. What is perhaps more significant, however, is the fact that, despite the general decline, the distribution of individual titers was still considerably above that observed before vaccination. The data need not be repeated here since they appear elsewhere. Until it becomes possible to define the exact significance of the various antibody levels in terms of immunity, one can only comment that, in the majority, the level of antibody at the end of one year was beyond the zone of greatest susceptibility. Thus, if level of antibody parallels the state of susceptibility, then the effectiveness of the vaccine employed is sufficient for at least one season, and perhaps longer.

This is supported by *direct* evidence gathered during the epidemic that occurred one year after the vaccination study was begun.[17] Although the intention was to compare the incidence of influenza among the alternately vaccinated and control individuals in each of the institution wards under study, this was not possible because of the low incidence and sporadic occurrence of disease in these groups. Fortunately, however, a sufficient number of wards was excluded from the immunization studies, and it was among these that sharp outbreaks occurred. It was therefore possible to compare the incidence of influenza in so-called "vaccinated" and "unvaccinated" wards. Striking differences were observed. There were 1319 persons residing on the 15 "unvaccinated" wards, and the incidence of influenza in this group was 12.4 per cent; whereas among the 1916 persons residing on the 20 "partially vaccinated" wards, the incidence of influenza was only 1.9 per cent. When considered in terms of the individual wards, it was found that the highest attack rate occurring among the "unvaccinated" wards was 29.1 per cent; whereas among the "partially vaccinated" wards the highest rate was 6.5 per cent. Eight of the 15 "unvaccinated" wards experienced incidence above 10.0 per cent, whereas none of the "partially vaccinated" wards had rates exceeding 6.5 per cent, and all but four had rates below 4.4 per cent.

It would appear from these data, in terms of comparable segregated vac-

cinated and unvaccinated populations rather than in terms of vaccinated and unvaccinated individuals, that vaccination had a significant effect for as long as a year at least. To some extent this parallels the observations made in nature—that epidemics of influenza A do not recur at intervals of less than two years. It may be that the mass immunizing effect of the epidemic takes that long to decline.

Reactions Accompanying the Administration of Vaccine. Reactions to influenza vaccine correspond in severity and character to reactions following typhoid vaccine. They are primarily attributable to the virus content.[18] In the studies referred to,[5, 11-15] approximately half of the vaccinated individuals had some complaints and about 1 to 2 per cent developed febrile reactions up to 101.5° F. within 24 hours of inoculation. Such symptoms usually last no longer than a day. At the site of inoculation, edema, redness and tenderness may develop in about 12 hours and persist for about a day or slightly longer. The local and systemic symptoms are related to the quantity of virus administered rather than to any non-virus impurities that are present.

One word of caution is warranted, and that is the danger of anaphylactic reactions in persons with *known* egg-sensitivity, who are given any vaccine of egg origin. The development of sensitivity to repeated inoculations seems to be less of a risk or no risk at all. An adult who has once been given an injection of vaccine originating from an egg, and this includes a good number of vaccines, is much less likely to have an acute reaction than one who is to have his first inoculation.

With respect to age variations, influenza vaccines of the degree of concentration spoken of here are practically untried in any significant series of children. The indications at present are that it must be used with care, and systemic reactions suggest that smaller dosages may be advisable.

Discussion

On the basis of the results of these studies carried out by the Commission on Influenza, the Surgeon General directed that plans be made to vaccinate the entire Army in the fall of 1945, using vaccine prepared in the same manner as that employed in the field studies. For the first time development of mass production as well as mass immunization with influenza vaccine was involved and was accomplished successfully.

In November and December 1945, a widespread epidemic of influenza B occurred. The program of vaccination of the Army provided the extraordinary opportunity for observing its effect on a large scale. Through a combination of circumstances at two universities [19, 20] it was possible to make careful comparisons between fully vaccinated groups of Army students and comparable groups of unvaccinated individuals. Under these conditions the ratio of cases, vaccinated versus unvaccinated, was 1 to 9. At one of the universities the incidence of hospital admissions for respiratory disease was 1.1 per cent among 600 vaccinated men, whereas among the 1100 unvaccinated

men it was 9.9 per cent. Moreover, infections of mild degree occurred in a high proportion of the unvaccinated group and almost not at all in the vaccinated group. Although it might be said that the vaccinated group escaped the epidemic by chance, it should be pointed out that results at both institutions were consistent and that these observations reflected the general trend in the vaccinated Army as compared with other comparable groups where vaccination had not been employed.

In view of certain impressions which have been created, one can comment that neither the results nor the program adopted by the Army was dependent upon the preparation of vaccine by Sharples' centrifugation. Little or no centrifuged vaccine was used in the Army vaccination program of 1945. Actually, the centrifugation studies to which this refers [21] did not come to light until after the results of the successful field trials against influenza A had been achieved. Evidence obtained thus far does not support the a priori contention that the more highly purified vaccine produces fewer reactions nor that it is a more effective antigen.

Although incontrovertible evidence is now available that the resistance of man to infection by the viruses of influenza A and B can be enhanced, it is also evident that the problem of controlling epidemics of influenza by means of immunization cannot be approached only from the viewpoint of affording individual protection. It is clear that the individual influences the mass effect, and that the mass effect influences the individual response. The problems of the future are to devise means for enhancing [22, 23] and prolonging individual protection and to extend our present knowledge into the field for the purpose of establishing the minimum requirements for preventing the epidemic phenomenon. When the latter has been accomplished, it may be found that the requirements for individual protection need not be as rigid as is assumed at present. Until such time, it would appear advisable to suggest that the protection of individuals should be practiced.

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HEPATIC INSUFFICIENCY. I. PATHOPHYSIOLOGY AND CLINICAL ASPECTS *

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Exposure to exotic diseases and infectious hepatitis of members of the armed forces necessitates reëvaluation of concepts of hepatic insufficiency by physicians. Recognition of relative hepatic insufficiency is not on a par with the diagnosis of insufficiency in other organs, and many physicians do not concern themselves with the liver until overt jaundice appears. Sensitive biochemical methods reveal that impaired liver function is far more common than previously suspected. The immense recuperative power of the liver masks the insufficiency until the parenchyma fails to eliminate bilirubin.

Mass wartime experience has firmly established the clinical and biochemical attributes of hepatic insufficiency in cases of hepatitis.[1-8] The similarity of biochemical, clinical and pathologic data in icteric and nonicteric phases of the disease has given impetus to the recognition of hitherto unrecognized forms of hepatic failure. Clinical endeavor has long been directed to the detection of concealed liver disease. Now thousands recovered from infectious hepatitis form a fruitful group of subjects to study the aftermath of this disease in relation to the development of hepatic insufficiency.

The quest for a single miracle test of liver function disturbance is now fully recognized as futile. The need for the use of a combination of suitable tests for assessment of hepatic failure is appreciated. Random choice of a battery of tests may also fail of this purpose. A careful selection of tests is indicated. A fixed group of tests may be recommended for general screening purposes. The proper selection of tests for investigative and clinical problems depends on the *type* and *stage* of hepatic insufficiency. The uses and limitations of the tests are determined by these factors. Specific physiologic defects determine the clinical aspects of liver failure. The stages of progressive failure must also be recognized. The proper selection of the laboratory tests is guided by the clinical evaluation of the symptoms and signs of liver failure in terms of type of pathophysiology and grade of liver insufficiency. These phases of the subject are developed in the following material. The methods of clinical diagnosis and the principles of treatment of liver insufficiency will be presented at a later date.

The Clinical Attributes of Hepatic Insufficiency

The symptoms and signs of hepatic insufficiency are often vague and correspond to those of many systemic diseases. In many instances they are

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secondary effects upon the liver. For example, a large share of digestive complaints present in heart failure are referable to impaired hepatic circulation, and liver disturbance may develop with menstruation, anesthesia, coryza, thyrotoxicosis, malaria, infectious mononucleosis, pneumococcus infections, trench foot, amebiasis, burns treated with tannic acid, and after sulfonamide therapy.

The clinical picture of hepatic insufficiency is found in publications dealing with fatty liver,[9] infectious hepatitis, subacute diffuse liver necrosis.[10] The clinical aspects of the compensated and decompensated stages of cirrhosis [11] contribute further to the picture of liver failure. Pre-icteric symptoms are present in 50 to 90 per cent of subjects with hepatitis and liver atrophy. Large numbers of cases of toxic and infectious hepatitis, however, go undetected because jaundice never develops or remains subclinical. Hepatic insufficiency is studied to advantage in this type of clinical material. Great dependence is placed on biochemical determinations to gauge the state of activity of the latent disease process.

The symptoms and signs encountered in pre- and post-icteric forms of hepatitis are representative of other forms of hepatic insufficiency. Profound anorexia, nausea and vomiting occur. Constipation and diarrhea are the rule, normal bowel movements exceptional. Epigastric distress, when present, is aggravated by exertion; a sudden jog or motion induces a sharp pain that radiates backward to the lumbar region. Most patients complain of great fatigability, mental depression, and low-grade bifrontal headache. A layman will describe the individual as being lazy and tired. There is disproportionate dyspnea on slight exertion. Each outbreak of hepatitis seems to be characterized by some distinctive features. In one group that followed vaccination, fatigue, depression, anemia and dermatitis were common. Some epidemics were marked by prodromal chills, fever and lymphadenopathy. Hepatomegaly varied in incidence. Some observers stressed normal size of spleen and liver. Itching was present in 5 per cent of cases during the pre-icteric phase in one group. Neurological complications have been emphasized in reports.[12, 13]

The symptomatology of *latent* liver disease often resembles that of chronic exhaustive states, so that a diagnosis of psychoneurosis [3, 6] is often entertained until jaundice appears. Patients who attempt physical activity find themselves unequal to the task. Jaundice may become apparent for the first time, reappear, or become accentuated. In military service the symptoms of masked subsiding hepatitis were labeled as neurasthenia, and individuals bearing them were credited with seeking easy assignments. Fatigue, exposure, emotional stress or actual trauma precipitated manifest jaundice, disclosing the latent hepatic insufficiency. It was most likely persistence of the disease, rather than a recurrence.

The absence or subsidence of jaundice may lead to clinical misconceptions. Although jaundice is important in focusing attention on the liver, its disappearance must not be assumed to mark cessation of liver damage. It is

difficult to determine the abatement of hepatitis without laboratory aids. Although hepatitis subsides rapidly in most individuals, a low-grade process may persist for months or years in some. Jaundice may reappear periodically during periods of physical or emotional distress. In about 0.2 to 0.5 per cent of cases, depending on the severity of the epidemic, hepatitis goes on to acute hepatic necrosis. It has been estimated in different series that 6 to 32 per cent of cases of cirrhosis result from infectious hepatitis with slow progression of the lesion. The recital of the latency and progression of the liver disease in significant numbers of individuals emphasizes the importance of recognition of hepatic insufficiency as a major clinical task.

Despite the varied symptomatology of hepatic insufficiency several clinical patterns are delineated. Jaundice and hepatosplenomegaly are common features. The associated symptom-complexes fall into at least five categories:

1. A clinical picture simulating a generalized infection, 'grippal' in nature, with its recovery phase of post-grippal asthenia. The presence of chills may arouse suspicion of cholangitis.

2. An enteric form in which gastrointestinal disturbances predominate. Anorexia, distaste for food, epigastric discomfort and intestinal motility disturbances are the chief complaints.

3. Neurologic-neuropsychiatric forms, marked by meningeal irritation, peripheral nerve disease, neuromuscular, neurocirculatory, and psychoneurotic complaints.

4. A nutritional deficiency state, evidenced by anemia, malnutrition, tendency to bleeding into the skin and from mucous membranes, weakness, subvitaminosis.

5. Cases marked by the clinical manifestations of portal failure: ascites, gastrointestinal bleeding, and dilated venous collaterals.

Applied Physiology

Unfortunately, there is no single index or test to gauge the competency of the liver. Study of hepatic insufficiency by biochemical and pathologic correlation, however, suggests four general considerations:

1. Reduction in efficiency is not symmetric: one or more functions can be severely impaired and others remain normal.

2. Hepatic insufficiency can exist without demonstrable histologic changes.

3. Hepatic reserve allows destruction of a major fraction of the cells without evidence of insufficiency. But relatively *minor* damage, involving *all* the cells, impairs functional efficiency.

4. Clinically, therefore, the symptoms of hepatic insufficiency may persist, long after the last biochemical evidence of impaired function can be demonstrated. Hepatosplenomegaly may, in turn, persist long after both the symptoms and impaired function are no longer apparent.

The Types of Functional Failure

Study of changes in hepatic function involves consideration of three elements: The *first* is a defect in the parenchymal cell itself. The *second* is a vascular defect that limits portal and arterial flow; and the *third* element is the failure of biliary drainage. Fulminating disease in the parenchymal cell may result in necrobiosis, while vascular insufficiency tends to produce atrophy.

Acute yellow atrophy is, in reality, acute, diffuse necrosis with loss of cellular units. The shrinking of liver size, following portal failure, readily results from atrophy of parenchymal units, nourished principally by unmixed portal blood. Prolonged disease of the parenchymal cells with the resulting change in architecture is usually followed by vascular failure. Thus, one finds combined defects where the disease is of long standing.

The metabolic functions of the liver are usually considered from the viewpoint of the foodstuff acted upon—namely: carbohydrate, protein, or fat, and not from the viewpoint of the mechanism of the function. The functions result from a chain of interrelated reactions. A single type of cell performs innumerable functions. Efficiency is secured by reducing the number of enzyme systems to a minimum. The so-called detoxication mechanism of the liver is not necessarily purposeful. The liver does not have a fixed formula ready for every new chemical presented to the body. Substances arriving through the portal circulation are treated in accordance with their chemical resemblance to physiologic substances. The liver acts as a barrier against toxic products formed in the intestine. Substances may be conjugated or oxidized. There is a common exchange of mechanisms for handling substances.

Many of the so-called toxic substances exert a deleterious action mainly by virtue of the fact that they resemble a nutrient and exclude that nutrient from being utilized by the cell. Furthermore, such antimetabolites may occupy a strategic crossroad, so to speak, and blockade a number of functions which utilize a key enzyme system.[14] Because of this the liver may be deficient in some functions, yet show normal efficiency otherwise.

1. *Hepatic Insufficiency of Parenchymatous Origin.* Congenital defects may provide situations which contribute to our knowledge of metabolic mechanisms. Cases have been reported of individuals who have inborn deficiencies that result in impairment of isolated liver functions. Von Gierke described a condition in which there was an unusual accumulation of glycogen in the liver. Most recent evidence suggests that it is due to an intracellular disturbance of the phosphorylase-phosphatase system which balances the synthesis and disintegration of glycogen in the liver. In another rare disease, chronic hypergalactosemia, the liver is unable to convert galactose to glycogen. The resulting galactosuria, hepatosplenomegaly, anemia, and albuminuria are diminished or lost when lactose and galactose are withheld

The presence of excess galactose in the blood inhibits glycogenolysis and produces hypoglycemia.

A condition in which there is an inborn defect in the excretion of bilirubin by the hepatic cells has been described as a constitutional hepatic dysfunction or familial hyperbilirubinemia.[15] Except for the periodic episodes of jaundice which these patients demonstrate, there has been no evidence of progression of the disease.

2. *Hepatic Insufficiency Resulting from Circulatory Changes in the Liver.* It has been pointed out that, in addition to the inherent functional efficiency of the parenchymal cell, the ultimate work performed is conditioned by the competency of the hepatic vascular elements and biliary passages. The relation of the double afferent blood supply to the hepatic architecture and the portion of the lobule nourished by portal vein and both portal vein and hepatic artery in the normal and diseased liver have been the subject of extensive study. Although the function of the hepatic cell itself is important in acute hepatitis and acute necrosis, with the development of cirrhosis in the more chronic forms of liver disease, the threat from the vascular lesion becomes preëminent. The prognostic significance of reduction of portal flow was accented by Mann's demonstration of the need of portal flow as a stimulus for regeneration.[16] Failure of the portal circulation, with portal hypertension, causes prehepatic deviation of nutrients into the caval circulatory system. The resulting nutritional deficiency produces secondary liver atrophy, comparable to that resulting from an Eck fistula. The hepatic cells become increasingly dependent on the blood from the hepatic artery, thus losing the *reciprocal* control of portal flow. Loss of this sluice mechanism changes conditions so that the parenchymal cell functions continuously instead of intermittently. When the lesion progresses and impedes hepatic artery flow, irreversible parenchymal failure obtains.

3. *Hepatic Insufficiency of Bile Duct Origin.** The metabolism of the bile pigments and their relation to hepatic insufficiency will not be discussed here. The defect lies in the liver cell or the channels leading bile from the liver. Resorbed stercobilin also enters into consideration in the problem of liver insufficiency.

The Grades of Functional Failure

It would be convenient if a solitary function was the first to be sacrificed in hepatic failure. But experience gained in the laboratory and clinic disclaims uniformity in the first function to lose efficiency as the liver becomes insufficient. The next best approach is to group the functions with reference to the order in which they are lost as the liver becomes progressively insufficient. The first group includes those functions which are[18] affected when the damage is *minor;* the second when it is *intermediate;* the third when the damage is *marked.* In this third group functional deficiency is detectable

* The rôle played by the Kupffer-stellate system in the pathogenesis or clinical aspects of hepatic insufficiency is important but awaits clarification.

only after marked damage is present; changes in this group are of especial prognostic significance. The arrangement, however, is subject to modification by the mechanism underlying the production of the insufficiency. Obstruction of the biliary tract, porto-caval shunt, bacterial or viral damage to the hepatic cell, functional overload, or blockade of the enzyme system may modify certain groups of functions. Attempts to differentiate intrahepatic and obstructive jaundice by tests are limited in value because establishment of biliary obstruction for any length of time usually produces hepatic cell dysfunction, yielding dissociated results.

I. *The Functions Modified in Relatively Minor Hepatic Insufficiency* (table 1 A).

1. The production of *bile salts* is among the early functions disturbed in liver cell injury. It is important to determine the cholic, desoxycholic, and conjugated forms, separately. The functions of synthesis, reclamation, conjugation and destruction all affect the level of excretion in the bile and urine and the blood level. There is evidence of production of abnormal types of bile salts in disease conditions.

2. Glucuronic acid production is diminished early in hepatic insufficiency. Alcohols, ketones, alkaloids and phenols are conjugated with glucuronic acid in the liver.

3. The ease of the determination of bilirubin in body fluids and the alteration of its solubility, diffusibility and reactivity after action by the liver have encouraged extensive study of this substance. Because of the hepatic

TABLE I

The Grades of Hepatic Insufficiency

A. Liver Dysfunction in *Minor* Grade Insufficiency
- Bile salt synthesis
- Glucuronic acid production and synthesis
- Detoxication mechanisms; organic substances
- Glycine synthesis
- Glycogen synthesis and storage
- Plasma protein synthesis; electrophoresis changes
- Bilirubin excretion
- Bromosulfothalein excretion

B. Liver Dysfunction in *Moderate* Grade Insufficiency
- Blood cholesterol; total and ester fraction
- Prothrombin-vitamin K response
- Alkaline phosphatase blood level
- Carotene-vitamin A synthesis, storage
- Thiamin-niacin metabolism
- Water metabolism
- Blood glucose homeostasis
- Estrogen inactivation
- Lipid mobilization and metabolism
- Iron-copper storage and utilization

C. Liver Dysfunction in *Severe* Grade Insufficiency
- Deamination of amino acids
- Glycogenolysis-neoglucogenesis
- Ketone body formation
- Electrolyte imbalance
- Blood volume control; pulmonary edema.

reserve, the ability to excrete an overload of bilirubin injected intravenously becomes impaired before an increase in the blood level is clinically manifest. Hence early diminished function can be demonstrated by the bilirubin tolerance test. The production of bilirubin is a function of the reticulo-endothelial system, and while the Kupffer cells participate in this, the parenchymal cell is involved in its excretion. Isolated excessive production of bilirubin theoretically does not produce jaundice, but, in clinical experience, hepatic damage soon ensues and clinical icterus results. This development of hepatic insufficiency with excessive bilirubin excretion explains the clinical limitations of the van den Bergh test, as compared with the theoretical considerations underlying this procedure.

4. The ability of the liver to excrete foreign dyes and pigments is also diminished early in hepatic insufficiency. Here again the presence of biliary obstruction will alter the interpretation of modified excretion. A variety of dyes are used by roentgenologists in visualization of the gall-bladder. The dye is administered by mouth, excreted by the bile, and concentrated in the gall-bladder. It is assumed that there is no hepatic insufficiency when a non-functioning gall-bladder is reported.

5. The so-called detoxication of some substances by the liver is diminished early in hepatic insufficiency. When cinchophen is administered by mouth, a portion is excreted in the urine as an intermediary oxidation product known as oxycinchophen. When the liver is insufficient the portion excreted as oxycinchophen increases. The ease of measuring the oxycinchophen and the fact that it is an intermediary step in the detoxication of cinchophen recommend this test.

6. The liver performs many functions essential in the protein economy. Although the exact mechanism of the storage of protein by the liver is not known, it is known that it is one of the functions that may be lost early in hepatic damage. There have been no reports of the injurious effect of excessive storage of protein in the liver, such as have been described for fat and glycogen. The rôle of the liver in the synthesis of the plasma proteins has been the subject of extensive study. The site of albumin synthesis has not been established, but there is no doubt that the major fraction is derived in the liver. The relative concentrations of the various protein constituents of plasma change early in hepatic insufficiency. Although these cannot be determined biochemically until the stage of insufficiency has progressed, sensitive physical methods such as electrophoresis reveal the early changes. These account in part for the applicability of various non-specific tests such as the Takata-Ara, cephalin-cholesterol flocculation, Weltmann coagulation, colloidal gold, and thymol turbidity reactions as tests of liver dysfunction.

7. The rate of synthesis of glycine is diminished early in hepatic insufficiency. This may be tested by determining the rate of conjugation of the glycine with benzoic acid as indicated by the excretion of hippuric acid. After oral ingestion of sodium benzoate one must take into account its rate and completeness of absorption, the availability of glycine for conjugation,

and the ability of the kidney to excrete the hippuric acid formed. Studies in which sodium benzoate and an excess of glycine have been injected intravenously have indicated that it is the synthesis of the glycine that is the limiting factor and not the rate of conjugation. Furthermore, a fraction of the benzoate is conjugated with glucuronic acid and excreted in the urine. Because of alternate pathways of conjugation, conclusions drawn from the excessive excretion of hippuric acid are subject to criticism. Although the kidney of normal individuals can excrete hippuric acid at two to three times the rate necessary, interpretation in individuals with damaged kidneys is hazardous.

8. The ability to store glycogen is diminished as hepatic insufficiency develops, but this is not easily measured. The function that can be estimated is the rate at which the various sugars are utilized or converted to glycogen. If one wished to name them in order of the ease with which they are converted to glycogen, levulose would be first, then glucose, and galactose last. D-lactate is converted to glycogen with greater ease than the sugars. The normal amount of lactate produced by metabolic processes can be utilized easily in minor hepatic insufficiency, and the blood lactate level does not rise. To show that there is a diminution of the ability of the liver to utilize lactate, a larger amount must be injected intravenously. When there is advanced liver damage the blood lactate does rise without a test with an overload. There are so many factors in the utilization of glucose that one would have to use tagged glucose to determine its utilization.

II. *Intermediate Group of Functions—Those Which Are Impaired as Liver Injury Progresses* (table 1 B).

1. When hepatic insufficiency is present the *cholesterol* and *cholesterol ester* content of the blood is diminished. However, in some varieties of toxic hepatitis and in the regenerative phase of hepatitis they may be elevated. In the present state of our knowledge, explanations of the lipid levels in the blood in hepatic disease follow circumstantial reasoning. Marked elevation of all the lipids of the blood is encountered in cases with long-standing stricture of the common duct, in which there is also marked liver damage.

2. Damage to the parenchymal cell is marked by inability to utilize vitamin K. In biliary obstruction, vitamin K may not be absorbed because of the lack of bile, and a diminished synthesis of prothrombin may result. When the parenchymal cell is damaged, the liver cannot synthesize prothrombin, even in the presence of adequate intake of vitamin K. The mechanism by which vitamin K regulates the synthesis of prothrombin is not known.

3. The serum alkaline phosphatase is elevated in obstructive jaundice, and it is normal or slightly elevated in parenchymal injury. However, in some cases of toxic hepatitis, such as follow arsphenamine administration, there is a marked elevation of the phosphatase. It is known that phosphatase is excreted in the bile and that there is a slight rise in the blood phosphatase after hepatectomy in dogs. The actual rôle of the parenchymal cell in phosphatase regulation is not known. Histochemical study of sections

of liver tissue shows a decrease in the phosphatase activity during hepatic necrosis. The activity is increased after starvation or protein depletion.

4. In hepatic insufficiency there is a reduction in the conversion of carotene to vitamin A. The vitamin A is stored in the Kupffer cells of the liver. Hence, when the liver is insufficient, the blood level of vitamin A may be low, the tolerance curve flat, and the dark adaptation reduced. In liver damage, limitation of the storage of vitamin C and thiamin has been noted.

5. The liver is involved in the regulation of water balance, and a defect in the ability to excrete added water by way of the kidney is noted in patients having hepatic insufficiency.

6. The part played by the liver in the regulation of the blood sugar is disturbed in hepatic insufficiency. In some cases there is hypoglycemia and a flat glucose tolerance curve, whereas in others there is a diabetic picture. It will be recalled that when synthalin was used in the treatment of diabetes, it was found that the reduction of blood sugar was the result of damage to the liver. Hyperglycemia and an elevated glucose tolerance curve are sometimes seen in hepatic insufficiency, simulating diabetes. If injury to the hepatic cells continues, hypoglycemia results.

7. There is a diminished destruction of estrogens in hepatic insufficiency. This probably accounts for the gynecomastia and testicular atrophy that is sometimes noted in cirrhosis of the liver.[18] Normal male patients will excrete about 10 per cent of an intramuscular dose of estrogen, whereas male patients suffering from cirrhosis of the liver may excrete up to 80 per cent of the injected quantity. It has been suggested that the liver also inactivates progesterone.

8. In some instances the injured liver loses its ability to discharge its fat, and although the lipotropic substances—choline, methionine, and lipocaic—aid in the prevention of fat deposition, they may fail to influence the injured liver laden with fat.

III. *Functions Which Are Modified When Hepatic Insufficiency Is Marked* (table 1 C).

These functions are fundamental to survival and are preserved as long as possible. Studies of the functions that are impaired early in hepatic damage are applicable in vivo; the functions that are impaired after marked damage can be studied in liver slices and isolated, perfused livers. It will also be observed that the latter functions are more fundamentally inherent in the cell and older phylogenetically.

1. Amino acids are deaminated in the liver with insignificant amounts deaminated in the kidney and intestinal musculature. Since the ammonia that is split off is not utilized, it is combined with carbon dioxide in the liver to form urea. In man, urea synthesis is limited to the liver. Both of these functions are impaired when hepatic insufficiency is advanced. The amino acid content of the blood may be elevated and the urea content diminished in advanced cirrhosis or acute liver atrophy. The tyrosine, found in the liver during liver autolysis, has been attributed partly to failure of deamination,

TABLE II

The Pathophysiology of the Common Symptoms and Signs of Hepatic Insufficiency

Clinical Symptom, Sign	Parenchymal Failure	Vascular Defect	Biliary Failure, Stasis
A. Primary Parenchymal Defect			
Anorexia	+	−	−
Fatigability	+	−	−
Myasthenia	+	−	−
Myalgia, Arthralgia	+	−	−
Dyspnea	+	−	−
Constipation, Diarrhea	+	−	−
Acneform rash	+	−	−
Anemia	+	−	−
Fetor hepaticus	+	−	−
Hepatic Coma	+	−	−
Mental Depression	+	−	−
Plasma Protein Changes: Hypoproteinemia, Hyperglobulinemia, Electrophoresis Pattern Changes, Ceph.-Chol. Flocculation Reaction, Colloidal Gold, Thymol Turbidity	+	−	−
B. Primary Vascular, Circulatory, Hemodynamic Defect			
Splenomegaly	−	+	−
Ascites	−	+	−
Venous Collaterals: Caput Medusae, Esophageal Varices, Hemorrhoids	−	+	−
Venous Bruit, Epigastrium	−	+	−
Hematemesis	−	+	−
C. Primary Biliary Stasis or Failure			
Xanthelasma	−	−	+
Pruritus	−	−	+
Nyctalopia	−	−	+
Osteomalacia, Osteoporosis	−	−	+
Constipation, Diarrhea	−	−	+
Steatorrhea	−	−	+
Bleeding tendency	−	−	+

TABLE II—*Continued*

Clinical Symptom, Sign	Parenchymal Failure	Vascular Defect	Biliary Failure, Stasis
D. *Parenchymal-Vascular Defects*			
Spider Angiomata	+	+	−
Edema Generalized Pulmonary	+	+	−
Hypervolemia	+	+	−
Hypoproteinemia	+	+	−
E. *Parenchymal-Biliary Defects*			
Jaundice	+	−	+
Steatorrhea	+	−	+
Epigastric Distress	+	−	+
Pruritus	+	−	+
'Cholemia'	+	−	+
Bleeding Tendency Hypoprothrombinemia	+	−	+

but mainly to autolysis of hepatic tissue. Intravenous injection of tyrosine or casein hydrolysate in suitable amounts, when deamination is inefficient, is followed by amino acid retention in the blood. The specific dynamic action of protein digestion is reduced *late* in liver injury. By the same reaction employed in converting the ammonia derived from deamination, the liver filters out the ammonia formed in the intestine and converts it to urea. Elevation of the blood ammonia in cirrhosis of the liver is disproportionate to the degree of failure of urea synthesis, because some ammonia passes by the liver via the porto-caval shunt.

2. The conversion of glycogen to glucose by the liver persists even in severe liver injury. Except in von Gierke's disease, amylase activity continues in the liver even after death. The hypoglycemia of terminal phases of liver disease is due to glycogen poverty.

3. The ability to oxidize fatty acids to ketones is not altered until late in hepatic insufficiency.

4. The regulation of electrolyte balance by the liver is disturbed in advanced liver disease. Similarly the part it plays in fluid balance is diminished. The factors that are changed in ascites and edema associated with liver disease are not fully defined.

5. The part played by the liver in the control of blood volume is altered in advanced liver disease.

The Clinical Aspects of Functional Defects

One functional defect, or two types of defects, may combine and produce the symptoms and signs of liver failure. The common symptoms and signs of liver disease have been correlated with the physiologic defects from which they likely arise (tables 2 a, 2 b, 2 c, 2 d, 2 e).

Summary

Wartime experience with infectious hepatitis has increased the significance of liver disease in clinical practice. The fact has been brought home that jaundice is merely one easily visible sign of liver disease. Serious forms of liver damage occur without overt jaundice. Early recognition and suitable treatment of hepatic insufficiency favor remission of the disease process. Relapses readily occur and lingering forms of hepatitis have been reported.

The symptoms and signs of liver insufficiency have been reviewed and classified.

Hepatic insufficiency, unfortunately, cannot be detected by a single test or procedure. The need for more elaborate measures is recognized. To meet this, pathophysiologic disturbances have been analyzed with an eye to bringing the laboratory procedures into closer agreement with the common clinical symptoms and signs of liver failure.

The fundamental types of physiologic defects underlying hepatic insufficiency have been enumerated. The functions of the liver have been graded according to progressively increasing degrees of failure—namely: *minor, moderate, severe.*

The symptoms and signs of liver disease have been tabulated according to their pathophysiologic mechanisms.

The ready clinical recognition of hepatic insufficiency is rapidly approaching realization. Tests and procedures for the detection and estimation of the various types and stages of hepatic insufficiency are available, and appropriate selection is guided by the knowledge of individual types of physiologic defects, the grades of liver failure and their connections with the common symptoms and signs of liver disease.

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COLORADO TICK FEVER*

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Introduction

In 1930 Becker [1] described a disease he called Colorado tick fever, which up to that time had been assumed to be a mild form of Rocky Mountain spotted fever. The only experimental basis for this differentiation was that he could not obtain symptoms nor the typical scrotal reaction of Rocky Mountain spotted fever in guinea pigs following inoculation of blood from these cases. In 1940 Topping, Cullyford and Davis [2] undertook a systematic study of Colorado tick fever. They found it to be apparently associated with the bite of the wood tick, *Dermacentor andersoni* Stiles as postulated by Becker, but did not prove this. Neither were they able to transmit the disease to animals nor determine the etiological agent. Their studies convinced them that Colorado tick fever was of frequent occurrence in Colorado. It has also been reported in other Western states.

Clinical

The individual with Colorado tick fever has always been in a tick infested area four to six days before the onset of symptoms. Usually a tick is found attached to the body. Prodromata are lacking as the disease has a sudden onset ushered in by chilly sensations. Generalized aching of the entire body with headache, deep ocular pain and lumbar backache are the prominent symptoms. Photophobia, anorexia, nausea and sometimes vomiting are a part of the syndrome. With the onset of symptoms, the temperature begins to rise, reaching its height of between 102 to 104° F. within 24 hours. There is a concurrent increase in the pulse rate. This attack lasts approximately two days to be followed by a symptom free phase of like duration. The temperature is usually subnormal during the remission. The second attack is like the first but may last a day longer. Either attack may be more severe than the other. Although this is the usual pattern, the attacks and remission may vary from one to four days. Single and triple attacks have been recorded, but these are rare. Physical examination reveals only a mild erythema and slight conjunctival injection. There is no exanthem. Complications or deaths have never been recorded. Treatment is symptomatic. For several days following the disappearance of symptoms, the individual may feel weak and tired, but is usually able to resume normal activities.

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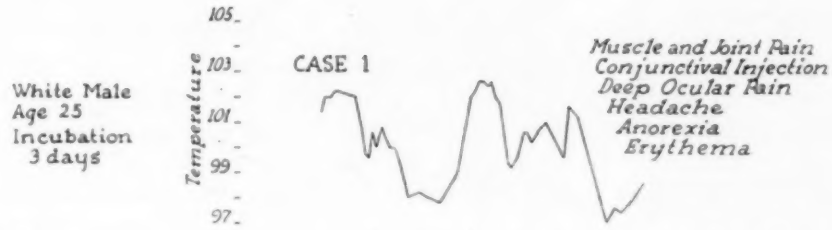
From the Department of Public Health and Laboratory Diagnosis, University of Colorado School of Medicine, Denver.

The significant laboratory findings are limited to the leukocytes. Typically the white blood cell count falls to between 2,000 and 3,000 cells per cubic millimeter, the lowest count being reached during the second attack. All types of the white blood cells are reduced in absolute numbers with the exception of the monocytes. There is a shift to the left in the granulocytes. The band forms may outnumber the segmented cells when the count is lowest. The white blood cell picture gradually returns to normal in four to seven days following clinical recovery.

Figures 1, 2 and 3 show the significant findings in three cases of this disease.

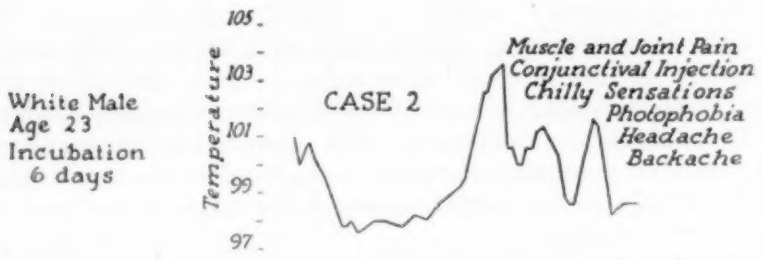


Days	1	2	3	4	5	6	7	8	9	10
Leucocytes in Thousands per cmm.	475	590	455	375	340	245	290	400	500	580
Segmenters %	62	47	42	52	39	41	37	37	42	37
Band Forms %	14	23	18	23	32	30	23	15	9	2
Lymphocytes %	14	20	32	20	21	25	35	42	40	51
Monocytes %	8	10	8	5	8	4	5	6	8	8
Eosinophils %	1								1	1
Basophils %	1									1

FIG. 1. Colorado tick fever in an experimental subject.

A STATEMENT OF THE PROBLEMS

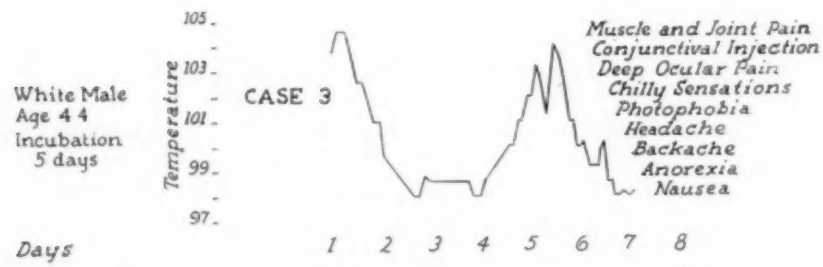
Although Becker and others were convinced that Colorado tick fever is a distinct disease entity, the fact that it is probably transmitted by the same vector as Rocky Mountain spotted fever caused the feeling to persist that it is a mild form of this disease. Because of its striking clinical and hematological similarity to dengue, certain investigators suggested the possibility that Colorado tick fever is tick-borne dengue. Before the question of these relationships could be settled, it was necessary to determine where the infectious agent might be found. It would then also be possible to make further studies as to immunity, transmission to an experimental animal, etiology and the mode of spread.



White Male
Age 23
Incubation
6 days

Days	1	2	3	4	5	6	7	8	9	10
Leucocytes in Thousands per c.mm.	355	270	280	270	180	170	200	190	370	405
Segmenters %	46	14	22	30	37	21	17	23	20	32
Band Forms %	17	13	16	15	29	22	15	15	13	10
Lymphocytes %	29	67	54	46	29	53	63	55	62	54
Monocytes %	8	4	7	7	5	4	4	6	4	3
Eosinophils %		2	1	1			1	1	1	1
Basophils %				1						

FIG. 2. A naturally acquired case of Colorado tick fever.



White Male
Age 44
Incubation
5 days

Days	1	2	3	4	5	6	7	8
Leucocytes in Thousands per c.mm.	5.60		4.50					3.35
Segmenters %	46		33					27
Band Forms %	26		28					18
Lymphocytes %	14		30					45
Monocytes %	13		8					10
Eosinophils %	1							
Basophils %			1					

FIG. 3. A naturally acquired case of Colorado tick fever.

Experimental Results

Human volunteers were used in an attempt to find the infectious agent. Sera taken from natural instances of the disease during the first or second attack caused typical Colorado tick fever when injected subcutaneously into these volunteers. A later experiment also proved the agent to be present in the blood during the remission.[4] Successive human to human transfers, the longest being a series of six, did not seem to increase or decrease the virulence of the disease although the incubation period was usually three instead of four to six days. It was during this phase of the work that the changes in the differential distribution of the white blood cells were first noted, a fact previously unrecorded.

There are no reports of an individual having the disease a second time. In order to test the immunity, three of the original volunteers were reinoculated with a different strain of the infectious agent nine to 12 months after the original infection. They did not develop the disease, indicating that Colorado tick fever confers at least a short immunity.[3] Several volunteers could not be infected. These individuals had lived in endemic areas for many years.

To test the assumption that Colorado tick fever is a mild manifestation of Rocky Mountain spotted fever, human volunteers were immunized against Rocky Mountain spotted fever with four instead of the recommended two doses of tick vaccine.[3] One month following the last dose, these vaccinated volunteers were inoculated with Colorado tick fever serum. The disease they developed was indistinguishable from naturally acquired Colorado tick fever. One of the natural cases we studied had been immunized against Rocky Mountain spotted fever three months before acquiring Colorado tick fever.[4] Two individuals who had had both diseases have also been brought to our attention[5]; another is reported by Shaffer.[6] Finally the fact that later work proved that Colorado tick fever is not a rickettsial infection confirms Becker's assumption that the disease is not a mild form of Rocky Mountain spotted fever.

Since clinically and hematologically Colorado tick fever and dengue are strikingly similar, their possible relationship remained to be elucidated. As both diseases confer at least a short immunity to themselves, each should protect against the other if they are identical. Six human subjects were inoculated with dengue and developed typical disease. Two were later reinoculated and found immune. The remaining four were injected with the infectious agent of Colorado tick fever. All developed typical disease with the exception of one individual who had previously lived in an endemic area. One volunteer was first inoculated with Colorado tick fever and later with dengue. He developed both diseases. These experiments seem to indicate that Colorado tick fever and dengue are distinct diseases.[7]

In order to make possible a wider latitude in the continuation of the

experimental work than was permitted by the use of volunteers, it was decided to attempt the infection of an experimental animal. We found the golden hamster (*Cricetus auratus*) to be susceptible. Evidence of infection was adduced by the finding that the white blood cell count is definitely lowered as it is in man, although there is no characteristic change in the differential count in these animals.[3] It was first necessary, however, to establish the normal blood cell values for the golden hamster. This was done on a series of 114 normal animals in which the white blood cell count was $8,088 \pm 1,773$ [8] as compared to $4,540 \pm 1,777$ in a group of 65 infected animals. As further proof of the successful infection of the hamster, serum from the seventh hamster transfer was also inoculated into a volunteer who developed typical Colorado tick fever.

In the early serial transfers of the infectious agent, the hamsters appeared normal, but beyond the twelfth passage, the animals began to die and a mortality of 25 to 50 per cent was common.[4]

Histologic studies of the tissues of infected animals revealed that the spleen was the only organ that showed variations from the normal. There were alterations in the cellular type and arrangement of the follicular lymphoid tissue as well as a partial or complete disappearance of the normal well defined follicular margin. Normal hamster serum carried through successive groups of animals failed to elicit these responses. The splenic reaction was first observed on the second day following inoculation, reached its height on the third day and continued through the fifth day.[9] This reaction occurred in approximately 80 per cent of a series of 522 infected hamsters and is more consistently found after the strain has been adapted to the animals by several passages.

Having infected the hamster, it was now possible to proceed to a determination of the etiology of Colorado tick fever. All attempts at visualization of the organism had failed. It could not be grown on any of the common laboratory media nor on chick embryo.[2, 4] It was logical to assume that the agent was a virus, and therefore filtration experiments were tried with gradacol membranes of known porosity. The agent was found to pass a 24 mμ membrane, although two passages were usually required in hamsters in order to elicit the typical white blood cell response. Such filtrates did not infect man. However, these same filtrates did cause characteristic human disease if they were first passed through hamsters.[10]

In order to obviate the possibility that hamster serum per se or some agent picked up from the serial passage of hamster serum might cause symptoms in man and hamsters similar to Colorado tick fever, the following experiment was done using animals selected at random from our colony. The serum of five normal animals was pooled and injected into 10 hamsters and this process repeated serially through 10 groups of approximately 10 animals each. The white blood cell counts and the splenic reactions in this series of animals were normal throughout. Furthermore, serum from the

tenth passage was injected into two volunteers who remained well but who later developed Colorado tick fever on being challenged with serum from a natural instance of the disease.

The infectious agent of Colorado tick fever is an extremely small virus, comparable in size to that of yellow fever and poliomyelitis, two of the smallest human infecting agents.

The virus of Colorado tick fever shows many interesting properties.[4] It is remarkably stable, surviving for at least three and a half years either in the ice compartment of an ordinary refrigerator or in a commercial deep freeze unit. It can be preserved by freezing and drying although the virus seems to be initially weakened by this procedure. The disease can be transmitted to the hamster in the usual dosage in dilutions of 1 : 1000. Healthy hamsters caged with sick animals do not acquire Colorado tick fever even after eating those that died of the disease.

The evidence for the tick transmission of Colorado tick fever is entirely circumstantial. The two original human volunteers fed adult male and female ticks for the duration of the disease. The progeny were carried through a complete cycle. Some of the nymphs and adults were fed separately on susceptible human subjects, but failed to transmit Colorado tick fever.[3] The experimental work going on at the present time on this phase of the problem has not progressed to the point where definite conclusions can be drawn.

It remains to develop a laboratory test that will confirm the clinical diagnosis. However, a diagnosis can be made with a high degree of accuracy based on the clinical history, course, and hematological study of each case. In Colorado the history of exposure to ticks, the dengue-like symptoms and fever curve are characteristic of no other disease, since dengue does not occur in this part of the United States.

Summary

Colorado tick fever is a virus disease, presumably tick-borne. It has been presented as a regional disease. Like Rocky Mountain spotted fever it may be found to occur much more extensively than is now supposed. It is a distinct disease entity related neither to Rocky Mountain spotted fever nor to dengue which it clinically and hematologically closely resembles.

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ASSOCIATION OF ACUTE PULMONARY LESIONS WITH INFECTIONS OF THE THROAT *

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IN a three year study of respiratory illness among soldiers, three groups of diseases have caused the great majority of hospital admissions, namely, exudative tonsillitis and pharyngitis, primary atypical pneumonia, and undifferentiated respiratory disease. Other specific diseases such as influenza and the contagious exanthemata constituted a small and easily recognized group. Investigation of the cases of exudative tonsillitis and pharyngitis disclosed that approximately 25 per cent of them had clinical features, bacteriological findings, and an antibody response indicative of streptococcal infection; another 25 per cent harbored β-hemolytic streptococci but did not have the clinical features or the antibody response characteristic of streptococcal infections. Half of the patients with exudative tonsillitis and pharyngitis had neither clinical, bacteriological, nor serological evidence of streptococcal infection and the cause of the illness remained unknown.[1] The second commonly encountered disease, primary atypical pneumonia, was recognized by its characteristic roentgenographic lesion and distinctive history, physical findings, and clinical course.[2] Undifferentiated acute respiratory disease was a diagnosis made by exclusion in patients who did not have roentgenographic evidence of a pulmonary lesion, and did not have streptococcal infection, or exudative tonsillitis and pharyngitis.

In the progress of these studies a number of patients have been encountered in whom pulmonary lesions demonstrable by roentgenograms have been associated with exudative tonsillitis or pharyngitis due to the streptococcus or of unknown cause. Instances have also been found of the association of pulmonary lesions with streptococcal infections not producing exudate in the throat.

These cases have been of interest from several points of view. They raised the question of whether or not two distinct etiologic entities were con-

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currently infecting the patients. Conversely, they might be explained as instances of pneumonia due to β-hemolytic streptococcus or other agents producing pulmonary lesions similar to those usually called primary atypical pneumonia. In the absence of specific tests or criteria for the diagnosis of primary atypical pneumonia, the problem cannot be settled at the present time. Nevertheless the cases themselves are thought to be of sufficient interest to warrant presentation of some illustrative examples.

Pulmonary Infiltration Associated with Exudative Pharyngitis Due to β-Hemolytic Streptococcus

The following three cases are representative of the group exhibiting clinical and laboratory evidence of streptococcal pharyngitis or tonsillitis associated with pulmonary infiltration of the type usually seen in primary atypical pneumonia.

Case 1. A 19-year-old soldier was admitted to the hospital on April 13, 1943, one week after induction in the Army, complaining of sore throat, cough, chest pain, feverishness, and headache. Four days before admission, he noted the onset of sore throat of moderate severity, followed by nasal obstruction and discharge, hard cough accompanied by the production of sputum, substernal discomfort, and hoarseness. Two days later, headache, feverishness, chilliness, malaise, and anorexia developed.

On initial examination on the fifth day of illness, the patient was only mildly ill. The pharyngeal and tonsillar mucosa were slightly injected and there were a few discrete spots of tonsillar exudate. The cervical lymph nodes were moderately en-

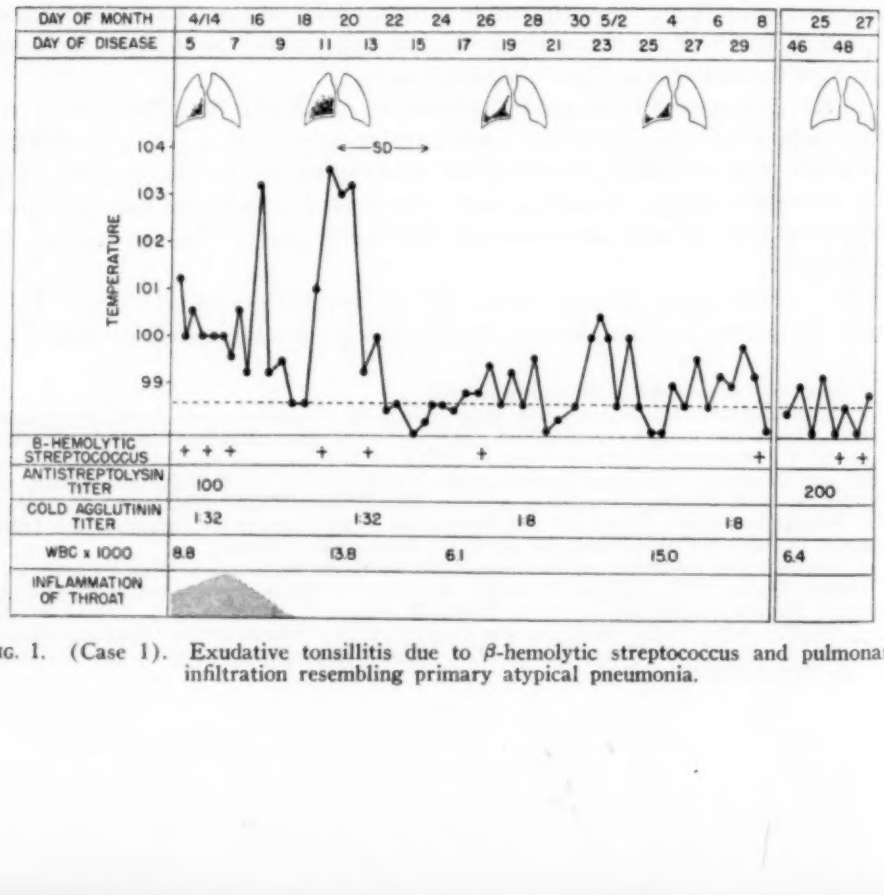

Fig. 1. (Case 1). Exudative tonsillitis due to β-hemolytic streptococcus and pulmonary infiltration resembling primary atypical pneumonia.

larged. β-hemolytic streptococci of group A, type 9, were recovered in throat cultures. The course of the illness and pertinent laboratory data are depicted in figure 1.

In the two days following hospital admission, the pharyngeal mucosa and particularly the soft palate became intensely red and edematous, presenting the appearance typical of peritonsillar cellulitis; without specific treatment this reaction subsided in a few days, as did the swelling of the lymph nodes.

A roentgenogram of the chest taken on the fifth day of illness revealed irregular hazy areas of increased density at the base of the right lung. Physical signs of pneumonia were not detected until the eighth day of illness. On the eleventh day of disease, the temperature rose to 104° F. at which time roentgenographic and physical findings indicated involvement of most of the right lower lobe. A blood culture taken at the height of the febrile reaction remained sterile. Sulfadiazine was administered in usual dosage for three days without apparent effect on the course of the pulmonary disease, although the temperature approached normal. The patient's subsequent course was consistent with atypical pneumonia, and was characterized by prolonged low-grade fever, slow clearing of the pulmonary lesion, and the production of copious amounts of mucopurulent sputum. A roentgenogram of the chest on the forty-eighth day of illness revealed completely clear lung fields.

Comment. This patient apparently had a simultaneous onset of pharyngitis and atypical pneumonia. Throat and sputum cultures contained β-hemolytic streptococci throughout the entire hospital course, and a rise in antistreptolysin titer in the serum was found. Whether the pulmonary lesion was caused by β-hemolytic streptococcus or whether the latter was a secondary invader complicating primary atypical pneumonia cannot be stated with certainty. The course of the pulmonary disease was certainly not of the type generally thought to be characteristic of hemolytic streptococcal pneumonia. The presence of cold agglutinins may be considered a point in favor of the view that the pulmonary lesion was due to primary atypical pneumonia.

Case 2. This 20-year-old soldier, with three months of military service, was admitted to the hospital on April 20, 1943 complaining of sore throat. The day before admission he developed a sore throat followed shortly by feverishness, chilliness, headache, malaise, and anorexia. At the time of initial examination he appeared mildly ill with signs of a mild streptococcal tonsillitis. β-hemolytic streptococci of group A, type 5, were recovered from throat cultures. The tonsils and soft palate were moderately swollen, the mucosa diffusely injected, and there were large confluent patches of exudate on the tonsils and uvula. The cervical lymph nodes were somewhat enlarged. The temperature record and pertinent laboratory data are recorded in figure 2.

Without specific treatment, the symptoms and signs of tonsillitis subsided in the course of four to five days. At about this time, however, the patient began to complain of nasal obstruction and discharge, cough, substernal pain, and hoarseness, and began to raise moderate amounts of mucopurulent sputum. He continued to run a low-grade fever which rose occasionally to 101° F. Roentgenograms of the paranasal sinuses and of the lungs revealed normal findings. On the fifteenth day of illness, however, a very small lesion in the costophrenic angle of the right lung was revealed by roentgenogram, and on the twenty-second day this shadow was seen more clearly. At this time, fine inspiratory râles were detected for the first time over the right lower lobe. Râles were heard daily thereafter until the patient left the hospital on sick furlough on the twenty-eighth day of illness. No chemotherapy was administered during the illness.

Comment. This patient had acute exudative tonsillitis from which β-hemolytic streptococci were recovered. He subsequently developed a rise in antistreptolysin titer. Although the pharyngeal lesion subsided promptly, low-grade fever continued and, in the third week of illness, physical and roentgenographic evidence of a pulmonary lesion was demonstrated. Although β-hemolytic streptococci were isolated from the sputum at this time, the development and course of the pulmonary lesion was in keeping with a diagnosis of primary atypical pneumonia. It is interesting, however, that in this patient, cold hemagglutinins did not develop.

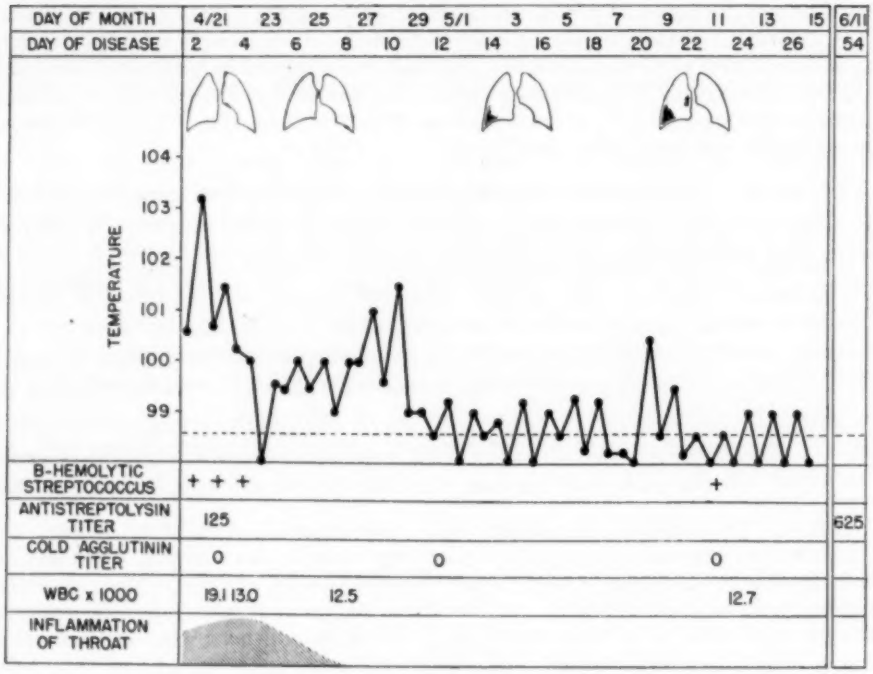

FIG. 2. (Case 2). Exudative tonsillitis due to β-hemolytic streptococcus and pulmonary infiltration resembling primary atypical pneumonia.

Case 3. This 20-year-old soldier, after one month in the Army, entered the hospital on May 12, 1943 complaining of chilliness, malaise, sore throat, and cough. He had mild symptoms of a cold for 10 days. On May 10 he developed sore throat, hoarseness, chilliness, feverishness, malaise, and headache.

On admission he appeared moderately ill. There was diffuse redness and edema of the soft palate. The pharynx and tonsils showed only injected vessels and a few pin point areas of exudate. The clinical impression was non-streptococcal exudative tonsillitis. The course of the illness and relevant laboratory data are shown in figure 3. The initial roentgenogram revealed no abnormalities in the lungs and the throat cultures on the first two hospital days did not contain β-hemolytic streptococci.

The patient appeared to be improving until the fifth day of illness, when it was noted that the tonsils and pharynx had become acutely inflamed and the cervical lymph nodes were enlarged and tender. Throat cultures now contained group A β-hemolytic

streptococci, type 3. The following day a diffuse scarlatinal rash appeared. The patient became quite ill and was given sulfadiazine from the eleventh to the sixteenth day of illness. During this time the appearance of the pharynx became normal and the skin rash faded.

On the eighteenth day of illness the patient developed substernal chest pain and fever, and physical examination revealed fine râles at the base of the right lung. A roentgenogram showed an area of increased density in this area. Sulfadiazine was again administered and the febrile reaction subsided. Fine râles were elicited by physical examination until the twenty-third day of illness. At the time of discharge, on the thirty-eighth day of disease, a roentgenogram of the chest showed a small area of increased density still present at the base of the right lung.

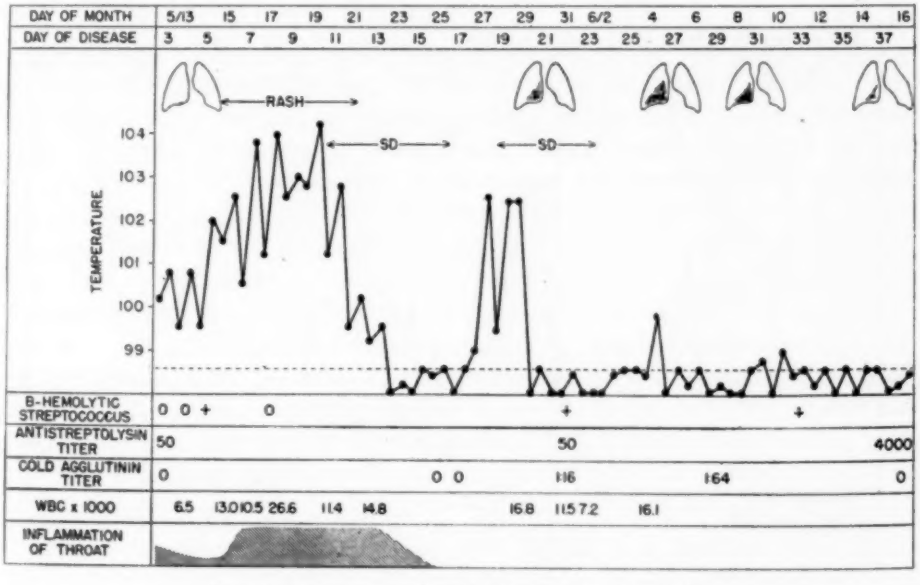

FIG. 3. (Case 3). Scarlet fever and pneumonia.

Comment. At the time of admission to the hospital this patient apparently had a non-streptococcal sore throat but subsequently developed scarlet fever and streptococcal pharyngitis. This was presumed to be an instance of hospital cross-infection. During convalescence from the streptococcal infection the physical and roentgenographic signs of pneumonia developed. Both streptococcal antibodies and cold hemagglutinins were later demonstrated in the patient's serum.

PULMONARY INFILTRATION ASSOCIATED WITH LABORATORY EVIDENCE OF STREPTOCOCCAL INFECTION

The following two cases are presented as additional instances of infection with β-hemolytic streptococci associated with pulmonary disease. In one instance (Case 4) the pulmonary lesion was demonstrated before the patient acquired his streptococcal infection.

Case 4 (figure 4). *First admission.* A 35-year-old white soldier with three months of military experience was admitted for the first time on March 19, 1944, with the complaint of cough and feverishness.

Illness began on March 17, with dry cough followed by feverishness, headache, anorexia, weakness, sore throat and hoarseness. On admission he appeared only mildly ill. The pharynx revealed no abnormalities and the chest was clear except for rhonchi. The temperature on admission was 100.2° F., rose to 102.6° F. that night and fell to normal on the fourth day. He was discharged on the sixth hospital day with a diagnosis of "common cold." Cough was still present on discharge but the other symptoms had abated. The day after admission fine râles were heard over the lower lobe of the right lung; these persisted for two more days but were not heard on discharge.

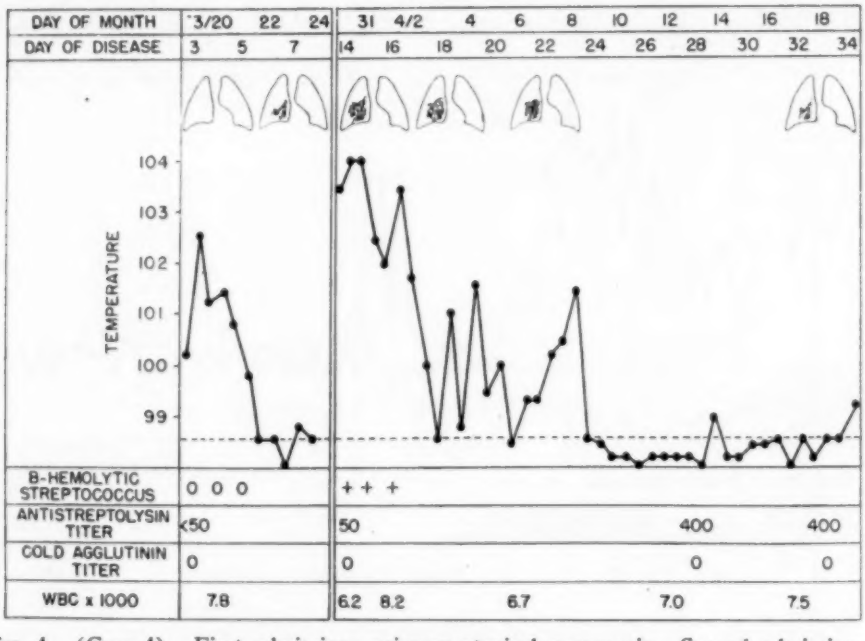

FIG. 4. (Case 4). First admission: primary atypical pneumonia. Second admission: primary atypical pneumonia and streptococcal pharyngitis.

The admission chest roentgenogram was normal but films on March 22 showed early peribronchial infiltration at the right cardiohepatic angle.

Throat cultures on March 19, 20, and 21 revealed no pathogenic organisms. On the day before discharge the bed next to him was occupied by a patient with hemolytic streptococcal pharyngitis. Unfortunately subsequent throat cultures were not made on the patient.

Second admission. The patient was readmitted on March 30, 1944, six days after leaving the hospital. In the interim he continued to cough and felt weak. He noted irritation and soreness of the throat. On March 26 he again became feverish and chilly and these symptoms persisted until he was readmitted.

Physical examination revealed no abnormal findings in the throat. There were fine and coarse râles over the lower lobe of the right lung and chest roentgenograms confirmed the presence of pulmonary infiltration. The temperature on admission was 103.4° F. and it remained elevated above 100° F. for a week. The patient was weak

and worn out, coughed and raised mucopurulent sputum but was not dyspneic or cyanotic. The pulse rate was not more than 100 even though the temperature was 104° F. The throat appeared benign. The course of the pneumonia, although protracted, was uneventful and recovery was eventually complete. No chemotherapy was administered during either hospital admission.

Total and differential leukocyte counts remained within normal limits during both hospital admissions.

Throat cultures on March 30, 31, and April 1, all contained moderate numbers of β-hemolytic streptococci of group A (not typable).

Sputum on April 1 contained a heavy growth (+++) of β-hemolytic streptococci of group A (not typable) and no other pathogenic bacteria.

During convalescence a diagnostic rise in antistreptolysin titer was demonstrated but cold hemagglutinins did not develop.

Comment. This case rather clearly demonstrates the concurrent existence of two separate diseases. In the first admission bacteriological study indicated freedom from streptococcal infection and at the same time the early stages of atypical pneumonia were present. Just before discharge he was exposed to a case of streptococcal infection in an adjacent bed and presumably was infected from that source. Premature return to duty may have caused an exacerbation of the pulmonary infection and on the second admission, a week later, he exhibited the characteristic course of a moderately severe case of atypical pneumonia. There was no clinical evidence of streptococcal infection. The antibody response could have been that of a streptococcal carrier.[8] Although the presence of streptococci in the throat and sputum suggested the diagnosis of streptococcal pneumonia, the clinical course was not characteristic of that infection. Moreover, if streptococcal pneumonia was present it must have been superimposed on primary atypical pneumonia since the latter clearly was present before the patient acquired his streptococci.

Case 5 (figure 5). An 18-year-old white soldier with less than one month's military service, was admitted to the hospital on March 23, 1944, complaining of chilliness and cough.

For about a week he had nasal obstruction and discharge and a non-productive cough. The day preceding admission he became feverish and had an exacerbation of the cough which was now associated with substernal discomfort and with the production of sputum. Later he became chilly, developed headache, felt weak, and noted sore throat.

On admission he appeared only mildly ill. The lungs were clear to physical examination. The uvula and pharynx were moderately injected and the former was edematous. The tonsils were large and swollen. However, there was no exudate and the appearance of the throat was not characteristic of streptococcal pharyngitis. The cervical lymph nodes were not enlarged or tender.

The redness and edema of the throat subsided the next day and he improved symptomatically. The maximum temperature of 103° F. was reached on the day after admission, but fever above 100° F. persisted for five days. On the third hospital day chest roentgenogram showed pulmonary infiltration in the left lower lobe, and at the same time râles were heard at the left lung base and these persisted for about one week. Convalescence was uneventful and the soldier was returned to duty on June 9.

Total and differential leukocyte counts were within the normal range during the illness.

Throat cultures on the first three hospital days showed β-hemolytic streptococci; the first and third contained group C organisms, the second group A, type 12. Sputum culture on March 30 revealed no significant pathogenic bacteria.

A diagnostic rise in antistreptolysin titer was demonstrated during convalescence but cold hemagglutinins did not develop.

Comment. In this case there appeared to be concurrent infection with atypical pneumonia and hemolytic streptococci of both groups A and C. The streptococcal infection was extremely mild, almost inapparent. It seemed unlikely that a streptococcal infection of this character would produce a bacterial pneumonia.

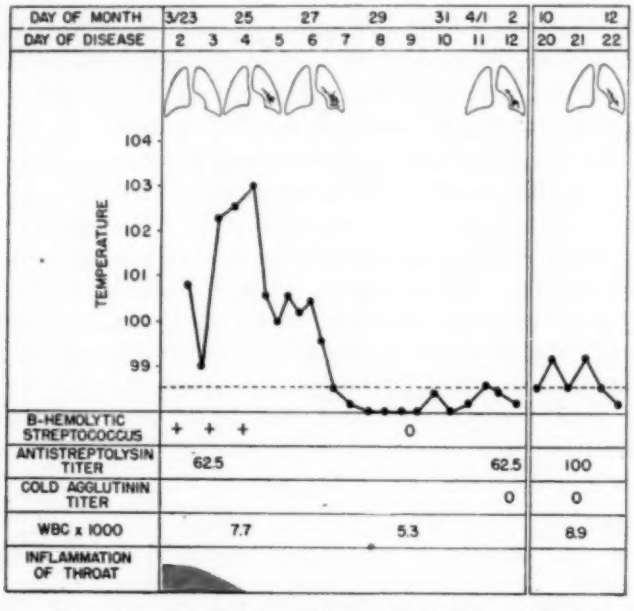

FIG. 5. (Case 5). Streptococcal pharyngitis and pulmonary infiltration resembling primary atypical pneumonia.

PULMONARY INFILTRATION ASSOCIATED WITH NON-STREPTOCOCCAL EXUDATIVE PHARYNGITIS AND TONSILLITIS

The final two cases presented are examples of non-streptococcal exudative pharyngitis and tonsillitis associated with pulmonary infiltration. In both of these cases the pharyngeal exudate persisted almost as long as the pulmonary lesion and may well have been etiologically related to it.

Case 6 (figure 6). A 23-year-old white soldier with two months of military service was admitted to the hospital on March 18, 1944, complaining of chilliness and fever.

Until the onset of the present symptoms he had been in good health. On the day before admission, he noted nasal stuffiness, and later in the day became chilly and then feverish.

On admission he did not appear seriously ill. The pharynx was moderately injected and the uvula and soft palate reddened and somewhat edematous. The lungs were clear and the physical examination otherwise negative. The temperature was 103.8° F.

The next day the pharyngeal and tonsillar mucous membranes were still only moderately injected but there was a large patch of confluent white exudate on the pharyngeal wall and several tiny spots of exudate on the tonsils. The tonsillar exudate increased in size so that by the sixth day of illness each tonsil was covered with a thick green, dirty-looking necrotic membrane having the appearance of Vincent's infection. On the same day, crackling râles were detected for the first time in the region of the left lung posteriorly and a roentgenogram revealed infiltration throughout the entire left midlung field.

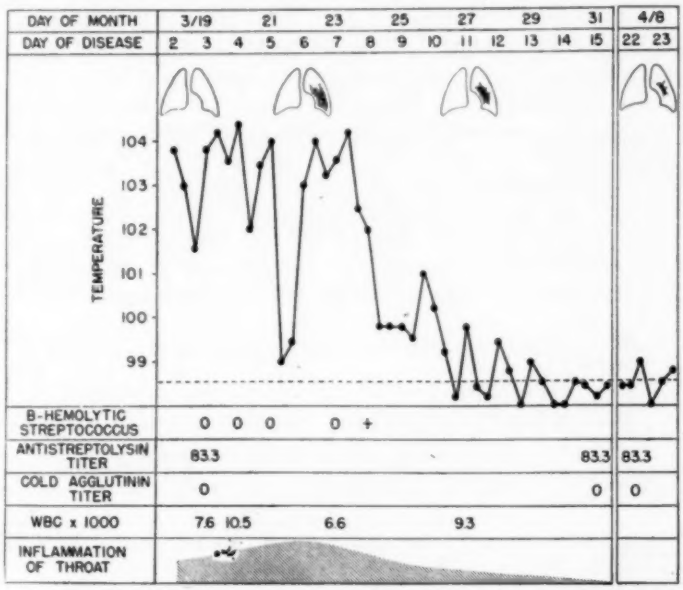

FIG. 6. (Case 6). Vincent's tonsillitis and pneumonia.

The patient maintained an elevation of temperature above 104° F. for four days, and above 100° for nine days. Despite the high fever, at no time did he appear seriously ill, and there was no dyspnea or cyanosis. The pulse was not elevated in proportion to temperature; while the latter was 104°, the pulse was 100.

Cough began on the sixth day of illness and was productive of only moderate amounts of mucopurulent sputum, which was never bloody, and was at no time foul-smelling. Likewise there was no fetor oris despite the presence of extensive exudate on the tonsils. The cervical lymph nodes were not enlarged or tender.

The patient slowly improved. The tonsillar exudate decreased in size until only small patches remained on the ninth day of illness, but the latter persisted for another week. The chest became clear to physical examination on the twenty-second day of illness.

Sulfadiazine was begun on the third hospital day but was discontinued within 24 hours because of albuminuria. Thereafter, aside from general supportive measures, only hydrogen peroxide and sodium perborate mouth washes were used.

Total and differential leukocyte counts were within normal limits throughout the illness.

Throat cultures on March 19, 20, 21 and 24 showed no significant pathogenic bacteria. A type 9 pneumococcus was present on several occasions, and a few colonies of group F β-hemolytic streptococci on one occasion. Fusiform bacilli and spirochetes in moderate numbers were found in smears of the tonsillar exudate. Cultures of the sputum revealed only normal flora.

No rise in antistreptolysin titer was found in convalescent phase sera. Cold hemagglutinins likewise were absent.

Comment. The development, progression, and resorption of the tonsillar exudate seemed to parallel the development and recession of the pulmonary lesion. This might suggest a single etiology for both lesions. On the contrary, the throat infection resembled Vincent's angina in appearance whereas the pulmonary lesion was not indicative of a lung infection caused by anaerobic organisms.

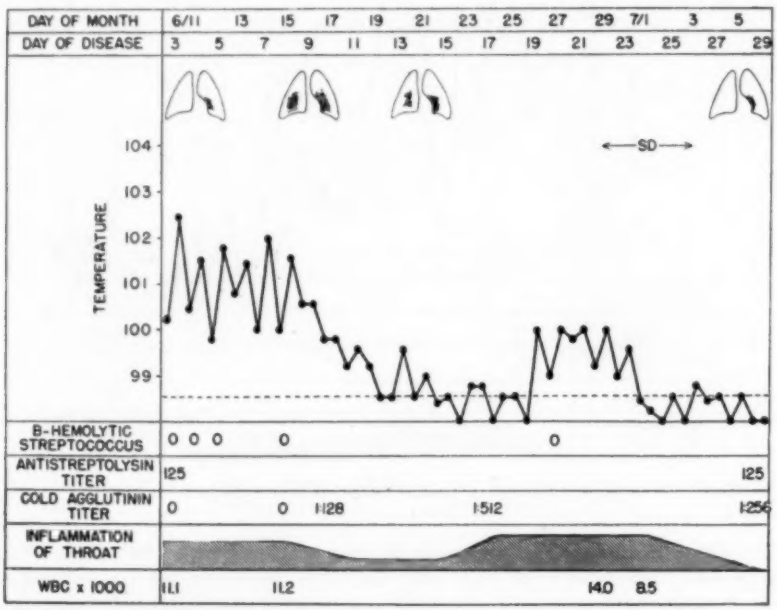

FIG. 7. (Case 7). Exudative tonsillitis and pharyngitis of unknown etiology and pulmonary infiltration resembling primary atypical pneumonia.

Case 7 (figure 7). A 19-year-old white soldier with three months of military service was hospitalized on June 10, 1943, complaining of cough, sore throat, headache, and fever.

Illness began on June 8 with sore throat and dry cough. The next day the patient developed a headache and shortly before admission became feverish and chilly, and complained of aching in the muscles of the back. The cough became productive and was accompanied by substernal distress.

The patient appeared moderately ill, and exhibited nasal obstruction and discharge and redness of the pharynx with prominent swollen red lymphoid follicles on the

posterior pharyngeal wall. The tonsils were small and moderately but diffusely injected, and had a small amount of streaky white exudate on their surface. The uvula was quite diffusely red and slightly edematous. The appearance of the throat was not typical of streptococcal pharyngitis. The cervical lymph nodes were not enlarged or tender. The lungs were clear and the rest of the physical examination yielded only normal findings. A small patch of pneumonic infiltration in the left lower lobe, along the cardiac margin, was seen in the chest roentgenogram obtained on admission.

The illness ran a protracted febrile course and throughout the patient appeared apathetic and listless, coughed and raised mucopurulent sputum and complained of anorexia and headache. The temperature varied between 100° and 102° F. during the first week, was below 99.2° for the next nine days, then rose again to 100° for four days, and finally returned to normal limits. Râles in the chest were first detected on the tenth day of illness. Clinically and by roentgenogram there was a spread of the pneumonia to involve both right and left lungs. The signs of inflammation in the throat, particularly the redness of the uvula and pharynx and the amount of exudate on the tonsils and on the posterior pharyngeal wall, seemed to wax and wane, being more intense during the two febrile peaks and subsiding in the afebrile interval. The patient was returned to duty on July 9, one month after admission, with the pharynx normal in appearance and the lungs clear. Sulfadiazine was given from June 29 to July 3.

The total leukocyte count was 11,100 per cu. mm. on admission but rose to 14,000 late in the course of the illness. Differential leukocyte counts were normal.

Throat cultures on June 10, 11, 12, 15, and 17 revealed only normal bacterial flora. Two blood cultures were sterile. Three sputum examinations for acid-fast bacilli were negative and smears of the sputum showed no fusiform bacilli or spirochetes.

No rise in titer of antistreptolysin was demonstrated but the cold hemagglutinin titer rose to 512.

Comment. In this instance the pharyngeal and tonsillar exudate and inflammation seemed to be an integral part of the disease since it waxed and waned with the febrile course and persisted as long as the pulmonary lesion.

Discussion

It is axiomatic in clinical practice to attempt whenever possible to explain all manifestations of illness in a patient on the basis of a single etiologic diagnosis. In the face of clinical, bacteriological, and serological evidence of streptococcal infection of the throat it is reasonable to assume that an associated pulmonary lesion is probably also due to streptococcal infection, and indeed, there is no undisputed method to refute that diagnosis. In no instance, however, among the cases presented, did the clinical features of the pneumonia fit the usually accepted picture of streptococcal pneumonia.[4, 5, 6] Although some of the cases had relatively high temperatures, they were of short duration and the patients did not appear profoundly ill. The pulse was relatively slow as compared with the temperature response. None of the patients exhibited more than minimal respiratory distress. None developed pleural effusions. During the course of the pneumonia the leukocyte count was normal or only moderately elevated. Sulfonamide therapy may perhaps have affected the febrile course but did not appear to shorten the duration of

the pulmonary disease and the course in untreated patients was similar to that in treated patients. If these cases did represent instances of streptococcal pneumonia, it is therefore necessary to revise current concepts of the clinical characteristics of that infection and to recognize that hemolytic streptococcus may cause a benign, transient, uncomplicated pulmonary infiltration similar in its clinical pattern to that produced by primary atypical pneumonia of unknown cause.

Streptococcal pneumonia appears to be a relatively uncommon complication of streptococcal pharyngitis. In a recent food-borne epidemic of septic sore throat involving 100 hospitalized patients, none developed pneumonia.[3] A similar absence of pneumonia following epidemic streptococcal pharyngitis has been reported by others.[7]

All of the clinical features of the pulmonary lesion in these cases which were regarded as not characteristic of streptococcal pneumonia were those which are commonly found in primary atypical pneumonia. The onset was relatively slow, the general condition of the patients good, the pulse slow despite high temperature, the pulmonary infiltration developed and resolved slowly, and the signs of respiratory embarrassment were minimal. Moreover, the physical signs and roentgenographic picture were entirely consistent with those usually found in primary atypical pneumonia.[2] The development of cold hemagglutinins in some of the cases supported this diagnosis. The failure to obtain cold hemagglutinins in some of the cases may be related to the age of the sera at the time the tests were performed.[8] Cold hemagglutinins were demonstrated in three of the four cases (1, 2, 3, and 7) in which the tests were performed within three months after the collection of the sera. In the three cases (4, 5, and 6) in which tests were delayed from 11 to 15 months after the specimens were obtained cold hemagglutinins were not found. In a previous study, however, it was found that even when freshly obtained sera were tested, less than half of the cases of atypical pneumonia developed cold hemagglutinins.[9]

The cases presented were selected from two study groups observed in two years during the spring of 1943 and 1944. In each group approximately 900 consecutive respiratory admissions from selected organizations were seen. All patients had roentgenograms of the chest; all were examined for the presence of exudate in the throat. Data were therefore at hand to determine the incidence of atypical pneumonia, streptococcal infections, and exudative tonsillitis and pharyngitis, both streptococcal and non-streptococcal. Atypical pneumonia accounted for 14 per cent of the admissions for respiratory disease during the first study and 7.5 per cent during the second study. In both years exudative pharyngitis and tonsillitis due to hemolytic streptococcus accounted for approximately 3.5 per cent of the admissions; exudative tonsillitis and pharyngitis of unknown cause were responsible for 6.5 per cent of admissions. With the data available, it was not possible to demonstrate any relationship, other than a fortuitous association, between the occurrence

of pulmonary infiltration and either streptococcal or non-streptococcal exudative tonsillitis. In this regard, two recent reports are of interest, describing what was believed to be a fortuitous association of malaria and primary atypical pneumonia.[10, 11]

The relation between non-streptococcal exudative tonsillitis and pharyngitis and pulmonary infiltrations, although it appeared statistically fortuitous, was clinically more obscure. In the course of these studies the impression was gained that in some instances the pharyngeal infection and the pulmonary lesion represented concurrent but independent infections. This seemed particularly likely in those instances in which exudate was present at onset and disappeared within a few days while the pulmonary lesion continued to evolve and persist for several weeks. Such a relationship was encountered in a number of cases. However, in the two cases described above the exudate in the throat persisted almost as long as the pulmonary lesion and seemed therefore to be more intimately related to it. This was particularly true of case *7*. In case 6, on the other hand, the clinical impression of the exudative lesion on the tonsils was Vincent's infection while the pulmonary lesion was entirely consistent with primary atypical pneumonia and inconsistent with the usual course of anaerobic infection of the lungs. Smith,[12] and Pierce and Field,[13] however, have pointed out that while the usual form of pulmonary fusospirochetosis is lung abscess and bronchiectasis, this may be preceded by acute pneumonitis which may resolve without reaching the stage of destruction of lung tissue. It is not possible, in the present case, to state whether the pulmonary and tonsillar lesions were independent or whether both were manifestations of fusospirochetal infection. This case of Vincent's angina was included in this report only as an illustrative example. In fact, however, Vincent's infections comprise a very small number of the group of cases termed exudative tonsillitis and pharyngitis of unknown etiology.[1]

One other possible association of respiratory diseases has been suspected, namely, the occurrence of both primary atypical pneumonia and acute undifferentiated respiratory disease in the same individual. Unfortunately there are no laboratory tests by which the latter diagnosis may be made and even its clinical recognition is dependent solely on exclusion of other entities. By the definition used of undifferentiated respiratory disease, this condition and atypical pneumonia are mutually exclusive. Nevertheless numerous instances have been encountered in which the patient was admitted to the hospital with what appeared to be acute undifferentiated respiratory disease only to develop signs of atypical pneumonia a week or 10 days later. Recent studies on human volunteers suggest that acute undifferentiated respiratory disease may be immunologically distinct from atypical pneumonia.[14] Epidemiological studies during certain years have demonstrated a parallel incidence of the two diseases during the winter months.[15] Until specific diagnoses can be made for both conditions the relationship between the two must remain speculative.

SUMMARY

Representative cases of the association of acute pulmonary infiltration and infections of the throat have been presented. Some of the upper respiratory infections were due to β-hemolytic streptococcus and others had exudate of non-streptococcal origin. The pulmonary lesions were of the type usually seen in primary atypical pneumonia. The relationship between the throat and pulmonary lesions was discussed. It was suggested that in some instances they may have been related while in others the association was probably fortuitous.

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CARBON TETRACHLORIDE POISONING; A REPORT OF ONE CASE WITH NECROPSY AND ONE NONFATAL CASE WITH CLINICAL LABORATORY STUDIES *

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Two recent cases in which the patients were admitted to the United States Naval Hospital, Oakland, California, and in one of which the termination was fatal, attest to the medical importance of carbon tetrachloride intoxication. As will be mentioned later in the reports of cases, both men, by ignoring simple precautions in the matter of ventilation, exposed themselves to toxic quantities of the volatilized chemical. That physicians generally are not sufficiently aware of the dangers of exposure to carbon tetrachloride is evidenced by the failure to establish a correct diagnosis prior to entry in this hospital in either case, despite an easily obtainable history and rather characteristic findings.

That carbon tetrachloride (tetrachlormethane, CCl_4) is toxic and occasionally fatal to both man and experimental animals has been realized at least since 1909.[1] Its lethal action on man is effected chiefly by means of damage to the kidney, as has been appreciated since the report of Smetana.[2] In addition to developing this thesis, Smetana discovered and reported 141 cases, with 39 fatalities, in reviewing the literature up to 1938. Subsequently, Quadland [3] cited approximately 300 cases, reported during the period 1932 to 1943, in nine of which the outcome was fatal. These resulted from occupational, but not necessarily industrial, use. He excluded from his series the nonindustrial fatality reported by Allison.[4] In addition, in the literature of 1943 and 1944 we have found reports of six fatalities, summarized in table 1; three fatalities reported in 1945 are also included in the table.[10, 11] Despite this impressive tabulation of the injurious action of carbon tetrachloride, its excellent solvent properties, coupled with its noninflammability and inexpensiveness, have maintained its widespread use in industry and in the home. That fatal or even serious poisoning does not occur in well-regulated industries is evidenced by the report of Smyth and Smyth [12] and the more recent account of Stewart and Witts.[13] A discussion in 1944 of industrial poisoning from carbon tetrachloride was concerned only with transient occurrences of nausea and vomiting presumably due to

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concentrations of less than the present legal standard maximum of 100 parts per 1,000,000 [14] in inspired air. Similarly, it will be seen in table 1 that most of the recent cases of fatal poisoning have occurred in isolated or individual use of carbon tetrachloride as contrasted to its use in industry.

The clinical picture of headache, nausea and vomiting, with occasional hematemesis, followed by mild icterus and later by oliguria, anuria and retention of nitrogen, is repeatedly described in the reports of cases appearing

TABLE I

Deaths Due to Carbon Tetrachloride and Reported in the Recent Literature

Reported by	Cases	Deaths	Circumstances in cases in which death occurred
Allison, B. R.[4]	2	1	The patient was an alcoholic who drank an unknown quantity of carbon tetrachloride by mistake.
Sanford, S. P.[5]	1	1	A seaman used a bottle of carbon tetrachloride to clean his hands, forearms and shoes, and died three hours later. Necropsy showed pulmonary edema.
Konwaler, B. E., and Noyes, C. B., Jr.[6]	3	1	Poisoning followed exposure in a closed compartment in which 1½ quarts of carbon tetrachloride had been volatilized. Two other persons simultaneously exposed recovered. (Necropsy)
Sherman, S. R., and Binder, C. F.[7]	4	1	The patient was cleaning a bomb sight in a room with poor ventilation and was overcome by fumes two or three times during the exposure. (Necropsy)
Forbes, J. R.[8]	3	1	French seamen; exposure in a small, poorly ventilated compartment while cleaning clothes in fire extinguisher fluid.
Willcutts, M. D.[9]	3	2	
Dillenberg, S. M., and Thompson, C. M.[10]	20	1	All cases occurred on a submarine, following volatilization of carbon tetrachloride. Fatality due to pulmonary edema nine days after exposure. (Necropsy)
Eddy, J. H., Jr.[11]	Unspecified	2	Ten patients, all ill enough to be hospitalized. Exposure occurred in process of manufacture of a land mine. "A tremendous amount of the chemical was vaporized in a closed room having no mechanical ventilation."

in the literature and is likewise exemplified by the reports which appear later in this paper. Pulmonary complications, such as edema and pneumonia, may occur as late as a week or more after exposure, as is emphasized by the reports of Smetana [2] and of Dillenberg and Thompson.[10] Although experimental proof is lacking, the inference is justified that some of the carbon tetrachloride is removed from the body by means of the expired air as well as by the kidney. This is said to be true of dogs, in which renal excretion is

TABLE II

Laboratory Data in Case 2*

Date, July	Blood chemical data									Blood pressure	Weight, pounds	Urine				Other tests
	C.C.	I.I.	CO_2	B.U.N.	N.P.N.	Cl.	P. Prot. Total	P. Prot. Albumin	Chol.			Quantity c.c.	U.N.	Alb.	Cells	
5	3	25.4								125/80		None				Kahn negative Hgb. 12.5 gm. WBC 11,600 Segs. 69%; Lympha. 31%
6		30.8		62.5			4.7	3.3	140			525 Specific gravity 1.010		2	Loaded with RBC	Chest x-ray negative Platelets 202,860
8		21.7		70.3	91.5		5.1		155	160/100		2,105	5.1	Neg.	RBC 2–4 HPF	EKG normal Serum calcium 10.7 U.U. 1:80 Clotting time 3½ min.
11	1	11.6	64			396				190/120		2,580 Specific gravity 1.015		Neg.		WBC 8,050, Segs. 72% Erythrocyte sedimentation rate 11 mm.
14				30.8		462	6.15	4.5		170/100	134¾	2,800	6.5	Neg.	RBC None	Creatinine 2.1 Hgb. 14.5 gm. RBC 4,420,000
19		15.2		22.8	51.7					140/90	123	3,000		Neg.	RBC None	Urea clearance 48% Visual fields and fundi normal
23	Neg.	11.7		17.2	40.9		8.1	4.2		138/80	123	3,100		Neg.	RBC None	Platelets 320,000
25										125/80		2,900		Neg.	RBC None	Urea clearance 82% Sulfobromophthalein retention 45 min. 20% 60 min. 5%

* Alb.—Qualitative urine test for protein. Sugar was not present in any specimen examined.
B.U.N.—Blood urea nitrogen, expressed as milligrams per 100 c.c. of blood.
C.C.—24 hour cephalin-cholesterol flocculation test; graded 1–4.
Chol.—Blood cholesterol.
Cl.—Blood chloride expressed as NaCl. Normal range 450–500.
Clotting time—Test tube method.
CO_2—Carbon dioxide combining power, c.c. per 100 c.c. of plasma.
EKG.—Electrocardiogram.
Hgb.—Hemoglobin (Haden-Hauser).
I.I.—Icteric index.
Lymphs.—Lymphocytes.
N.P.N.—Nonprotein nitrogen expressed as milligrams per 100 c.c. of serum.
Platelets—Method of Fonio.
P. Prot.—Plasma proteins.
RBC—Red blood cells.
Segs.—Segmented cells.
Serum calcium—Expressed as milligrams per cent.
Sedimentation rate—Cutler method.
U.N.—Urine urea nitrogen in grams per 24 hours.
U.U.—Urine urobilinogen in dilution (ratio).
WBC—White blood cells.

minimal and renal pathologic changes are correspondingly not conspicuous.[15] Further, while anuria or oliguria is the primary physiologic disturbance in man, the development of pulmonary edema is often the immediate cause of death.

Return of the damaged organs to their normal state has been presumed to follow clinical recovery. That this is actually true would seem established by the thorough investigation by Corcoran, Taylor and Page [16] of one case of recovery from the poisoning, and by the case of Simon,[17] in which necropsy 10 months after recovery from the poisoning did not reveal any residual signs of the intoxication, death being due to an unrelated cardiac disease.

Our second case, in which the diagnosis was established soon after admission of the patient, was rather thoroughly studied by means of hepatic and renal functional studies, blood chemical examinations and observation of blood pressure and weight. These findings are summarized in table 2. The early rise of blood pressure to a level of 190 mm. of mercury systolic and 120 mm. diastolic, with a subsequent fall to normal, is of some interest. The fall of blood pressure occurred coincidentally with a loss of weight, which in turn reflected the clinical disappearance of edema.

Case Reports

Case 1. An enlisted man, 24 years of age, became ill on the evening of February 6, 1945. At this time he was nauseated and vomited. The following morning he was free of symptoms but later on the same day he had a sudden chill, which was followed by fever and increasing nausea. By the morning of February 8 he complained of pain in the vicinity of both kidneys and was passing grossly bloody urine. He was admitted to the hospital the next day. On admission his temperature was 100° F., pulse 100, respirations 22, blood pressure 138 mm. of mercury systolic and 80 mm. diastolic. His face was flushed and he was vomiting bile-stained liquid. The abdomen was diffusely tender and there was bilateral tenderness of the costovertebral angles. There was no edema of the extremities nor clinical evidence of jaundice.

At this time a history of daily exposure over a period of six months to carbon tetrachloride in a large, open vat was obtained. The patient also admitted the rather liberal use of alcohol. On the day before the onset of his symptoms, which happened to be rainy, he had shut himself in his car while he cleaned his uniform and the upholstery of the car with carbon tetrachloride.

Laboratory studies after admission showed that leukocytes numbered 15,800 per cu. mm. of blood with 86 per cent segmented and 7 per cent band forms. Erythrocytes numbered 4,300,000 per cu. mm. of blood. The urine was loaded with erythrocytes and contained albumin in maximal quantities. The concentration of nonprotein nitrogen was 90 mg. per 100 c.c. of serum, that of chlorides was 396 mg. per 100 c.c. of plasma and the carbon dioxide combining power was 67 vol. per cent per 100 c.c. of plasma. The prothrombin time was 73 per cent of normal; the cephalin-cholesterol flocculation was reported to be weakly positive. On the second day in the hospital the patient was visibly jaundiced and the icteric index was recorded as 58 units.

The patient was placed in an oxygen tent on admission and fluids containing 300 gm. of glucose and 1,000 c.c. of amigen were administered intravenously each day. Physiologic saline solution was given as needed to maintain blood chlorides within the normal range. Vitamins C, K and B complex (betalin) were included in the foregoing solutions. In spite of this treatment, the patient pursued an unfavorable course,

Cyl.—Cylindruria.
N.P.N.—Nonprotein nitrogen expressed as milligrams per 100 c.c. of serum.
U.U.—Urine urobilinogen in dilution (ratio).
WBC—White blood cells.
Chol.—Blood cholesterol.
Cl.—Blood chloride expressed as NaCl. Normal range 450-500.

vomiting persisted and severe oliguria developed. He appeared drowsy, although mentally he was reasonably clear. The icterus gradually diminished, but the prothrombin time dropped to 50 per cent of normal, indicating progressively increasing hepatic damage. Erythrocytes disappeared from the urine but the daily output of urine fell below 100 c.c. The nonprotein nitrogen level rose to 174 mg. per 100 c.c. of serum. On the sixth hospital day the patient's face became edematous and the fluid intake was accordingly reduced to 1,500 c.c. daily. During the night of February 15, he complained of failing vision and retinoscopy showed a minimal degree of papilledema. Two hours later he became delirious and a series of clonic convulsive seizures developed. His temperature was recorded as 101.4° F. A spinal tap showed clear fluid under increased pressure. On the following morning he coughed up a small amount of blood-tinged frothy sputum and thereafter there was clinical and roentgenologic evidence of bilateral pneumonia. He died the following afternoon.

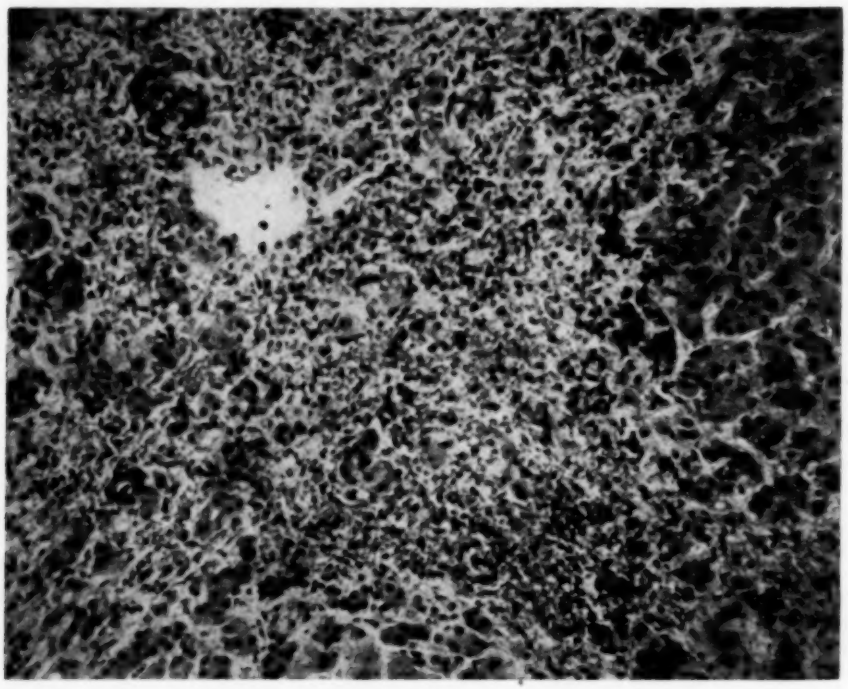

FIG. 1. Focal necrosis of liver, mostly in lobular centers, with advanced autolysis and loss of cell structure. Fairly heavy infiltration of inflammatory cells, largely neutrophiles.

Necropsy. The body was that of a well-developed white man. There was slight pitting edema of both ankles and the face was also edematous. Both conjunctivae were moderately edematous and definitely icteric. Bilateral pleural effusions were present with approximately 100 c.c. of clear fluid on the left and 150 c.c. of slightly yellowish, cloudy fluid on the right. Both lungs were definitely heavier than normal, the right weighing 1,115 gm. and the left 1,096 gm. On section, the parenchyma bulged slightly above the cut surface and an excess of free fluid escaped from the cut surfaces of all lobes. Small patches of pneumonic consolidation were present within the right upper lobe and diffusely scattered throughout both lobes of the left lung. The liver weighed 1,784 gm. and presented a mottled appearance. It was yellowish red. Both kidneys were enlarged, the left weighing 218 gm. and the right 294 gm.

The capsules stripped easily from both cortices, revealing smooth, yellowish surfaces. On section, the surfaces were greasy and yellowish gray, the differentiation between cortex and medullary portions being relatively indistinct.

Microscopically the most marked changes were observed in the liver and the kidneys. Scattered throughout the liver (figure 1) were foci of necrosis, mostly located about the lobular centers but in some places extending through the midzonal region to the periphery of the lobules. The hepatic cells in the centers of the affected portions showed advanced autolytic changes with complete loss of structure of many of the cells. The loss of supporting hepatic cells in affected regions allowed marked dilatation of the hepatic sinusoids, all of which were packed with erythrocytes. Many large macrophages were scattered throughout the necrotic regions and these contained ingested pigment granules. There was early proliferation of fibrocytes throughout the lobules of the liver but no apparent regeneration of hepatic cells was noted in any

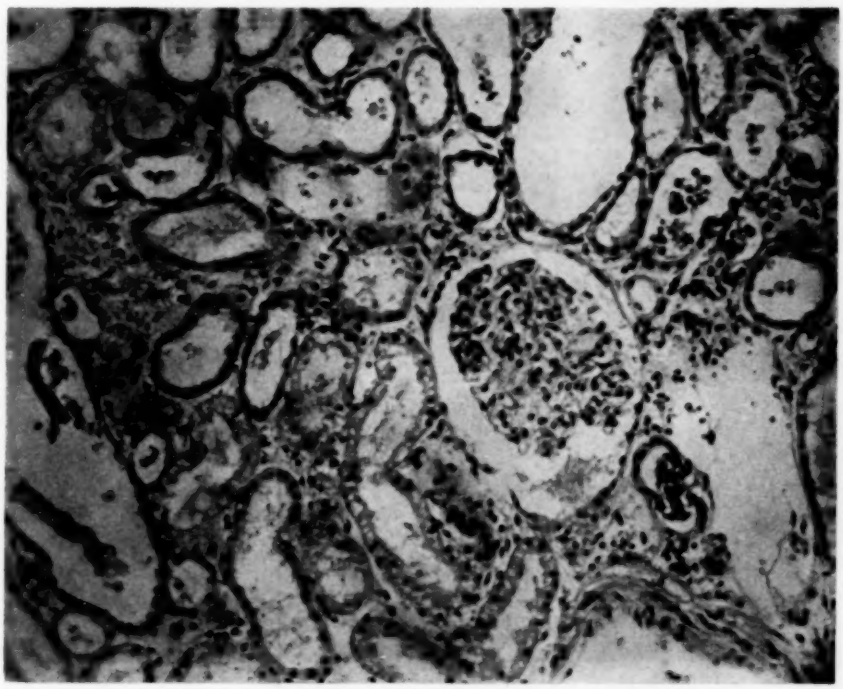

FIG. 2. Note destruction of renal tubule cells, with loss of nuclei and desquamation of cells.

sections studied. There was no evidence of proliferation in the bile ducts in the affected regions. Inflammatory cells, particularly neutrophiles, were infiltrated throughout the affected regions. Many focal collections of lymphocytes were also present about some of the smaller bile ducts. Fat stains showed lipoid droplets within the cytoplasm of many of the hepatic cells, especially at the periphery of the regions of focal necrosis.

Microscopically there were no glomerular changes in the kidneys (figure 2) except for some deposition of debris within the glomerular capsules. However, in both convoluted tubules and the loops of Henle there was marked destruction of the tubular epithelium. The cells were granular and many were completely degenerated. Numerous droplets of lipoid material were also demonstrable in the majority of the tubular cells on special staining.

The spleen (figure 3) presented regions of early necrosis in the central portion of some of the germinal centers, characterized by cellular destruction and early proliferation of fibrocytes with an increase of inflammatory products in these regions.

Microscopically, the lesions in the liver appeared to be the older. Those in the kidney appeared to be more recent, corresponding to the clinical course in this particular case. The splenic lesions were interesting, being similar to those demonstrated in cases of acute epidemic hepatitis by Wood.[18] In this case the splenic lesions were much less advanced than the lesions in Wood's cases, perhaps because the hepatic damage was not nearly as extensive.

Case 2. An enlisted man, 22 years of age, on the afternoon of June 30, 1945, spent an hour in an inadequately ventilated ship's compartment, measuring 20 by 12 by 10 feet, cleaning his uniform with a pint of carbon tetrachloride; he could not be sure how much was volatilized. Two other men who spent brief periods in the com-

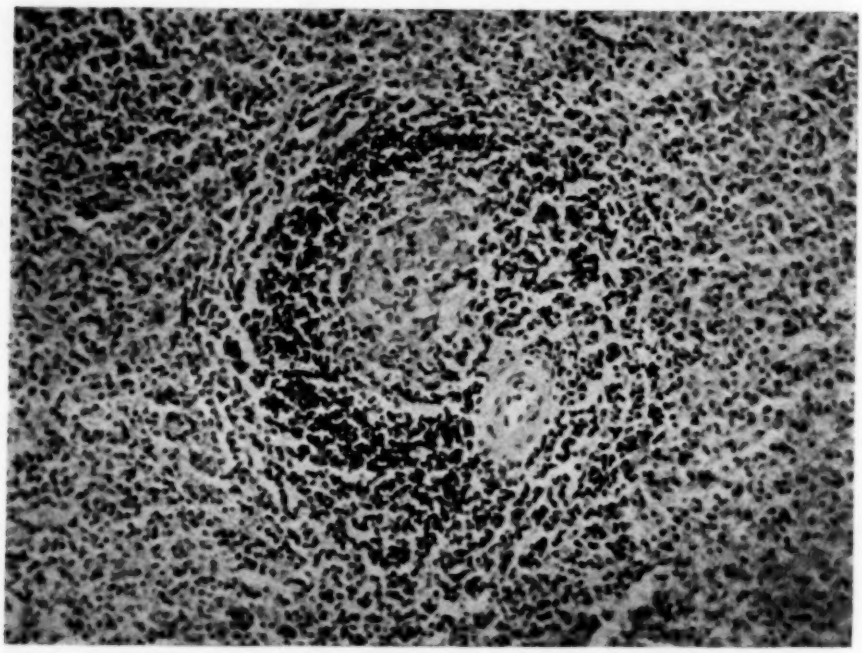

FIG. 3. Small regions of necrosis in germinal centers of spleen.

partment did not suffer ill effects. The patient was recovering from an infection of the upper part of the respiratory tract and it was at first difficult to distinguish the symptoms of that condition from the early effects of his exposure; subsequent developments, however, left no doubt that a toxic quantity of the chemical had been inhaled. The patient did not note any startling effects for 24 hours, during which time he ingested an allegedly small quantity of alcohol. The following day, 48 hours after the exposure to carbon tetrachloride, a headache, a temperature of 101° F. and protracted vomiting with hematemesis developed. He was transferred to the hospital on July 5.

On admission his temperature was 100° F.; the pulse was 90; the respiratory rate 25 per minute; the blood pressure 125 mm. of mercury systolic and 80 mm. diastolic. Physical examination showed a drowsy patient, who was vomiting re-

peatedly. There was a left subconjunctival hemorrhage. The liver was questionably palpable and the upper part of the abdomen diffusely tender. The patient was anuric during the first 24 hours; urinalysis on the following day revealed albumin and erythrocytes in quantity. By the second day facial edema was obvious and laboratory tests showed evidence of both hepatic damage and retention of nitrogen.

During the next week the edema markedly increased and then rapidly subsided. The blood pressure rose to a high point of 190 mm. of mercury systolic and 120 mm. diastolic, remained at this level for some days and returned to normal after three weeks. The urinary volume, which at first was very small, gradually increased to normal, although the urea content of the urine remained low. Concomitantly the patient lost weight and felt subjectively improved. The temperature was elevated in the evening to 100° F. until the tenth day in the hospital. Table 2 summarizes the laboratory data. It will be noted that electrocardiograms taken during the period of hypertension did not show any abnormalities and that roentgenographic examination of the thorax did not reveal any pathologic changes. It is of interest, in view of the report of Wirtschafter,[19] that the visual fields were not altered. One month after the patient's exposure, when clinical recovery was apparently complete, the concentration of urea in the blood was normal, as was the urea clearance. However, the sulfobromophthalein liver functional test, with a dose of 5 mg. per kilogram of body weight, showed abnormal retention (20 per cent at 45 minutes and 5 per cent at 60 minutes).

Despite the anuria and edema, solution of dextrose, saline solution and amigen were administered intravenously and, since there was an increasing output of urine, administration was continued until the third day in the hospital, when the patient was able to retain liquids given orally. Vitamins C, B and K were administered as in the previous case. The protracted vomiting was relieved after the stomach had been thoroughly washed with solution of sodium bicarbonate. Thereafter, a full diet high in carbohydrate and protein was given with the addition of 1 gm. of choline hydrochloride three times a day. The occipital headache present from the onset outlasted all other symptoms as well as signs of renal insufficiency; 50 per cent solution of glucose given intravenously did not relieve it. Six weeks after admission the patient was transferred to another hospital for a month's convalescence prior to return to duty.

Based primarily on the work of Minot and Cutler,[20] who noted that low calcium levels increased susceptibility to carbon tetrachloride poisoning, calcium gluconate is frequently administered intravenously in treating acute carbon tetrachloride poisoning. In addition, the usual supportive measures, oxygen and intravenously administered fluids should be employed. When anuria occurs, the physician faces the dilemma of the need for fluids and the patient's inability to excrete them. Confronted with this, Hagen and his associates [21] employed diathermy over the renal region and felt that this was instrumental in the favorable outcome in their case. Although portal cirrhosis due to carbon tetrachloride has been described,[22] hepatic damage is usually a minor part of the problem with reference to human beings. The amino acid methionine and lipotropic substances, such as choline, are being given a clinical trial in mitigating the hepatic damage [23] and appear to have some promise.

Comment

Data are presented on two cases of carbon tetrachloride intoxication, in one of which the termination was fatal. The rôle of alcohol as an adjuvant

to the toxicity of this compound is suggested in both cases. In view of the widespread and almost indiscriminate use of this solvent the likelihood of encountering future cases is great. The diagnosis is made by observing combined hepatic and renal damage in a patient giving a history of recent or prolonged exposure to this compound. The clinical phenomenon most to be feared is progressive oliguria or anuria. Treatment consists in administration of specific nutriments for the damaged liver and the provision of adequate fluids to counteract the loss by vomiting and to improve renal elimination. Administration of oxygen is thought by some to be of benefit and should be used with penicillin in the not uncommon event of pneumonia. Obviously the best and most effective treatment is prophylaxis; this consists simply in never using carbon tetrachloride without adequate ventilation.

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REITER'S DISEASE WITH PROLONGED AURICULO-VENTRICULAR CONDUCTION *

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IN a recent study of two cases that revealed a combination of features suggesting the diagnosis of Reiter's disease, transient auriculoventricular conduction defects were observed in the electrocardiographic tracings. These appear to be the first instances in which morbid effects upon the myocardium have been demonstrated during the course of this disease. Although the nature and pathogenesis of the cardiac involvement are yet to be clarified, recognition of such myocardial manifestations should dispel confusion in differentiating this obscure syndrome from other diseases.

Since the publication of the first report of Reiter's disease in 1916,[1] communications relating to this syndrome have appeared at irregular intervals. Only 45 cases were reported up to the moment of Lever and Crawford's contribution.[2] In many of these, however, the diagnosis had to be accepted hesitatingly since the diagnostic triad failed to evolve completely; in others, inconclusive bacteriologic search failed to eliminate a gonococcic or other infectious cause. A recent addition of three more cases was made by Colby.[3] Although the reports have been sparse and predominantly of continental origin, it is quite likely that the disease is not as rare as the literature may indicate.

Reiter's disease is a self-limited illness of undetermined etiology that is characterized by the appearance of a triad of major manifestations consisting of urethritis, conjunctivitis, and arthritis. With one exception,[2] all of the reported cases have occurred in young male adults. Acute urethritis or conjunctivitis is usually the first manifestation and within a period of four to eight weeks evolution of the triad is complete. The arthritis, however, may initiate the clinical onset. The purulent urethral discharge is attended by burning, increased frequency of micturition, meatal itching, and terminal hematuria. The conjunctivitis is, likewise, purulent but sticky. Superficial punctate keratitis is a frequent concomitant finding. Varying arthralgias of a migratory character may precede the polyarthritis. The weight-bearing joints are usually subject to inflammatory invasion although the syndrome may emerge with conspicuously disabling monarticular involvement. The common joints to be affected are the knees, ankles, wrists, hips, and the elbows, but the metatarsophalangeal, sternoclavicular and temporomandibular joints and segments of the cervical spine are not immune. The symptoms and the clinical appearances of the diseased articulations are similar to those of infectious origin. The arthritis is of longer duration than the conjunctivitis or urethritis and reluctance of the offended joints to sub-

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side prolongs the period of active disease. Although permanent joint destruction has not been seen, clinical and roentgenologic changes of a rheumatoid character have been reported.[2] The chemical and cytologic alterations of the aspirated synovial fluid resemble those found in the specific infectious arthritides.[4] The accompanying fever is moderate and chills are unusual. The course of the disease is self-terminated within one to five months, but recurrences of the entire triad or efflorescences of any of its elements may appear months or years after the initial onset. On the other hand, the conjunctivitis or urethritis may abate and recur one or more times during the course of activity. Complete recovery without sequelae or residual signs may be expected. Penicillin and the sulfonamides are considered therapeutically ineffective.

In a disease that awaits a better exposition of the pathogenesis, it is difficult to consider any manifestation as a complication. Indeed, extension of the disease processes to adjacent organs is exceedingly common and, occasionally, severe enough to dominate the entire clinical picture. In addition to the conjunctivitis and keratitis, other frequently recognizable ocular manifestations are episcleritis, iritis and iridocyclitis. The genitourinary involvement is not confined to the urethra, for catarrhal prostatitis, prostatic abscesses, vesiculitis, and hemorrhagic cystitis may be observed. Hydronephrosis, pyelonephritis, and ureteral obstruction may alter the common pattern of Reiter's disease to demand prompt consideration of surgical relief. Ulcerations about the meatal orifice, on the glans and behind the corona appear shallow and circinate with an exudative, crusting or dry surface. The oral lesions are characterized by erythema of the buccal mucous membranes, vesicle formation and, finally, denudation. Pharyngeal congestion, superficial glossitis, and a fine vesicular eruption of the lips may suddenly or insidiously become evident. The development of hyperkeratotic scales, particularly over the bony prominences, may make the skin eruption indistinguishable from gonorrheal keratosis blennorrhagica. Obviously such dermatitis, in the presence of urethritis, conjunctivitis, and arthritis makes differentiation of Reiter's disease from venereal keratosis blennorrhagica dependent solely upon careful and complete bacteriologic investigations. Hemorrhagic puncta or vesicles on the skin may antedate the keratotic lesions. Like the conjunctival and urethral inflammations, exacerbations and remissions of the dermal lesions may occur. Roentgenograms of the involved joints may show not only demineralization of varying degree, but also circumscribed areas of subchondral decalcification, periosteal proliferation, and narrowing of the joint spaces. Extreme difficulty may be encountered in separating these changes from those exhibited in rheumatoid arthritis.

The laboratory findings are not of diagnostic significance. The white blood cell counts fluctuate between 10,000 and 20,000 during the active state of the disease and the sedimentation rates are rapid. Pyuria, albuminuria and hematuria characterize the urinary findings on gross or microscopic

examination. Numerous pus cells can be found in the prostatic expressions. The bacteriologic, immunologic and microscopic studies of the exudates, tissues, lining membranes, and blood and cavity fluids do not contribute any pathognomonic findings.

Although the inflammatory phenomena lead one to assume that the disease is of an infectious nature, bacteriologic and immunologic studies have not uncovered the causative pathogenic agent. In Reiter's original investigation a spirochete was obtained from the blood of the subject; hence the designation of the disease by the title, "Spirochetosis Arthritica." Subsequent investigations, however, have invalidated the assumption that any spirillum could be related to the disease process. In spite of the striking similarity of Reiter's disease to systemic gonorrhea, smears and cultures of exudates from the genito-urinary tract, the conjunctival secretions and aspirated joint fluids have uniformly failed to reveal the presence of gonococci; blood cultures and urine cultures have not grown gonococcal colonies; and complement fixation tests performed at various stages of the disease have not disclosed any increased titers of specific antibodies. Agglutination reactions for *B. abortus* and brucellergin skin tests have presented negative results. Agglutination tests for dysentery strains have, in a similar manner, proved negative. Inclusion bodies have not been discovered in stained scrapings of the conjunctival, urethral or synovial membranes. Specific organisms could not be identified in smears from the oral and penile lesions. Cultures of macerated synovial tissue have been found sterile and inoculations of various animals have produced unsuccessful results. An extensive and detailed search by Bauer and Engelman [4] for specific bacterial or virus bodies was entirely fruitless.

The etiology has been further obscured by impressions derived from clinical observations. Beiglböck [5a] postulated that the disease was fundamentally an allergic manifestation with the genito-urinary, ocular and skeletal systems chiefly participating. The association of conjunctivitis, arthritis and balanitis with positive intradermal reactions to gonococcus vaccine in patients afflicted with gonorrheal urethritis has extended and supported this conception. Sherman, Bluementhal and Heidenreich [6] concluded that a toxo-allergic mechanism could effect superimposed ophthalmic, dermal, and arthropathic responses in bacteriologically proved gonorrhea. Clinical experience prompted Epstein and Chambers [7] to believe that oral, corneal and cutaneous lesions might be allergic manifestations when associated with gonorrheal urethritis. It must be emphasized, however, that the gonococcus could readily be identified in these cases, whereas in Reiter's disease such an etiology has never been established. To imply, then, that Reiter's disease is a transitional form of gonorrhea, the outcome of an infection wherein the causative agent has undergone morphologic alterations defying identification, is entirely speculative and untenable. Nor can one unreservedly accept Manson-Bahr's contention [5b] that the entire syndrome is related to dysenteric polyarthritis with superimposed toxic features.

Case Reports

Case 1. A 20-year old white male was entirely well until March 10, 1945 when aching of the left ankle appeared. For the following six days the affected joint showed surface heat, redness, and tenderness; motion and weight bearing became increasingly painful. On March 16, itching and smarting of both eyes were sensed and within 24 hours congestion, photophobia and a mucopurulent discharge developed. Simultaneously, a purulent urethral discharge appeared. The inflamed left ankle became increasingly worse and both knees became involved.

The family history was not contributory. Measles, scarlet fever, and chickenpox were the only previous illnesses. Sexual exposure was vehemently denied.

Although urethral smears on three successive days were negative for gonococci, 10 intramuscular injections of penicillin were administered at intervals of three hours, and penicillin solution was instilled into the conjunctival sacs every three hours for a period of four days. At the end of this time the eye symptoms abated and for the continuing urethral discharge and polyarthritis another course of 10 intramuscular penicillin injections was given. On March 27 the bilateral conjunctivitis recurred while the urethritis spontaneously vanished.

Hospital observation was undertaken March 28 for the mucopurulent conjunctivitis, bilateral superficial punctate keratitis, and the arthritis of the knees and left ankle. During the first four days, the temperature fluctuated between 96.8° and 100° F. and the pulse between 68 and 102. One drop of 4 per cent homatropine was instilled into each eye and metaphen ointment was applied continuously. At the end of the first week the conjunctivitis and keratitis cleared, the left ankle seemingly resolved but the knees remained swollen and painful. A distant apical systolic murmur was then detected for the first time. The urine sediment contained numerous clumps of pus cells; albuminuria (2 plus) was found; and the specific gravity measured 1.026. The white blood cell count was 11,100 of which 60 per cent were polynuclears, 34 per cent lymphocytes, and 4 per cent monocytes; the red blood cell count revealed 4,100,000 cells and the hemoglobin content was 82 per cent. The sedimentation rate on admission was 21 mm. (Wintrobe) and on April 16 was 30 mm. Electrocardiograms taken on April 1 and 15 exhibited PR intervals of .22 second and .24 second with rates of 92 and 88 respectively (figure 1). On April 26 the skin surrounding the urethral meatus became reddened; two days later a yellow-brown crust on an erythematous base about 1.5 cm. in diameter appeared immediately proximal to the glans. No pain, itching, or bleeding was experienced. The inflamed joints persisted throughout the entire course.

On May 11, 1945 hospital transfer was effected. The subject appeared chronically ill, emaciated, pale and unable to maintain the erect posture owing to pain and weakness of the lower extremities. The conjunctivae were normal in appearance; ophthalmoscopic examination was negative. Membranes of the hard and soft palates were sites of many pin-point vesicles surrounded by adjacent erythema; the tongue revealed several painless, denuded, sharply marginated, coalescent areas on the dorsal and lateral surfaces; the pharynx was coated by a mucopurulent, post-nasal discharge. Mastication and deglutition could be accomplished asymptomatically. The heart was regular, the rate was 120, and no abnormalities could be detected; the blood pressure was 116 mm. Hg systolic and 74 mm. diastolic. A diffuse, shotty lymph node enlargement could be demonstrated in the anterior and posterior cervical, the epitrochlear, axillary and inguinal regions; splenomegaly or hepatomegaly was not found. A circular erythematous base, partly covered by yellow crusts, extended about the urethral orifice for a distance of .5 cm. Immediately proximal to the corona on the right dorsal surface, a non-indurated, painless, superficial ulcer about 1.5 cm. in diameter with a clean base was visible. Both knee joints were enlarged and an increased amount of fluid in the left suprapatellar area could be palpated; the left ankle appeared

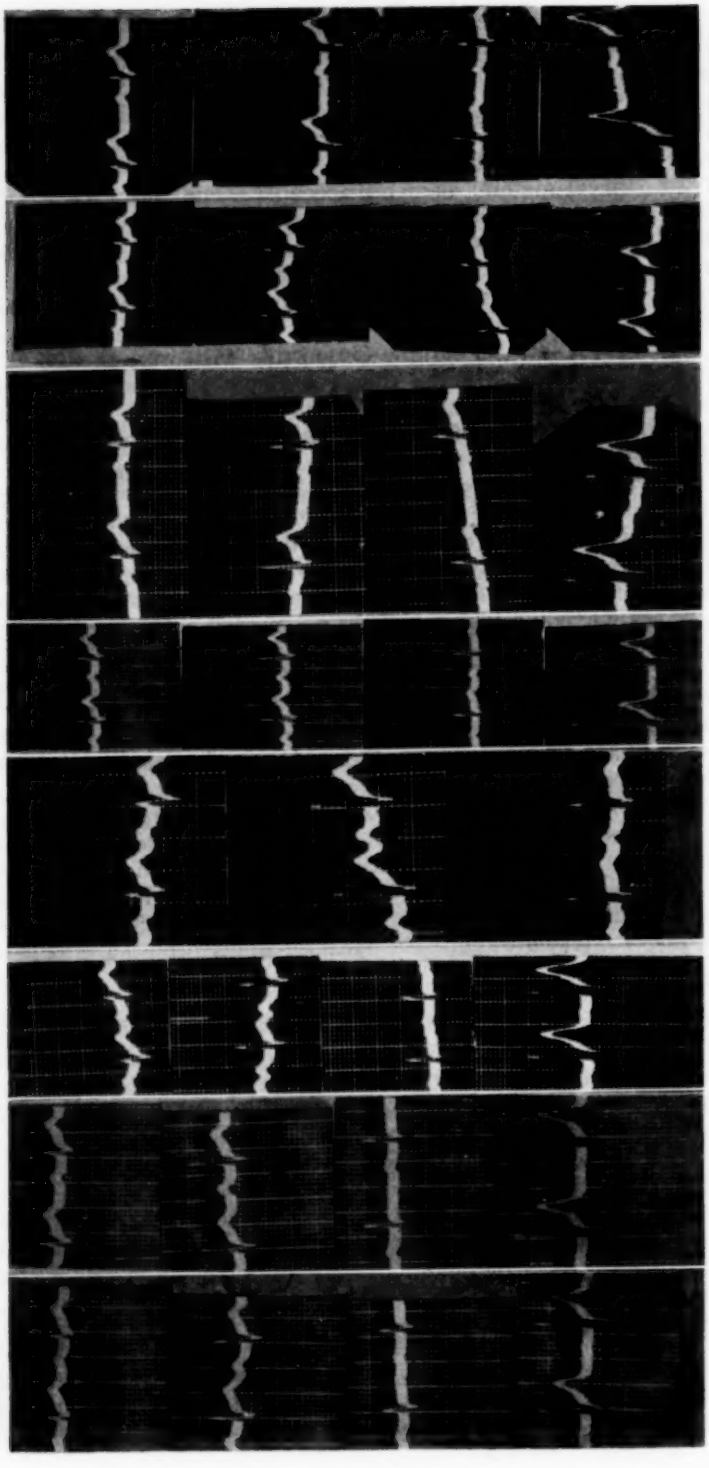

FIG. 1.

swollen. Painless motion could be executed in the involved joints, but both thighs and calves showed atrophy of the muscles attended by weakness and marked fatigability. An urethral discharge could not be expressed but the prostate was of a boggy consistency. The soles of both feet were covered with considerable keratotic deposits.

The arthritic condition improved slowly with radiant heat therapy and massage. Ambulation was undertaken with increasing ease and strength, although the swelling and stiffness of the joints persisted for four weeks. The thigh and calf muscles gradually increased in tone and size. The vesicular lesions of the oral membranes disappeared within a few days. In spite of the daily ingestion of 10 mg. of thiamine chloride, 150 mg. of nicotinamide and multiple vitamin capsules, the erythematous blush on the hard and soft palates persisted. During the third week an erythematous patch over the left buccal membrane erupted and a clean, painless, superficial ulcer 1 cm. in diameter appeared opposite the third upper right molar tooth. The denuded areas of the tongue remained unaltered in appearance. Yellow-brown scales adjacent to the meatus and over the ulcer proximal to the glans were desquamated but continued to reappear at irregular intervals; penicillin solutions applied to the penile lesions failed to effect any response. During the first week of June, non-tender vesicles of millet-seed size erupted on both lips but disappeared spontaneously within three days.

The laboratory findings were not informative. Urethral smears repeatedly failed to show any gram-negative, intracellular diplococci. The urine sediment contained 15 to 50 white blood cells under high-power fields; the specific gravity ranged between 1.016 and 1.028; the urea clearance was 102 per cent of average; cultures of the urine recovered hemolytic *Staphylococcus aureus*. The prostatic secretion contained many white blood cells but no organisms resembling the gonococcus. Cultures of the prostatic fluid yielded colonies of staphylococci and streptococci. Several smears of the meatal and shaft lesions showed no spirochetes, Ducrey bacilli, or Donovan bodies; a few gram positive diplococci were found. On several occasions, Kahn and Wassermann tests were performed but none was positive; the Frei, tuberculin and brucellergin skin tests were negative. No response was obtained to the intracutaneous test for Ducrey bacillus infection. All white blood cell counts during the six weeks of hospitalization varied between 4,750 and 8,000 with normal differential counts; the red blood cells and hemoglobin remained at normal levels. The serum protein content was 6.5 gm. per 100 c.c. and the albumin and globulin fractions were 4.6 and 1.8 gm. respectively. The Westergren sedimentation rate was 32 mm. on admission, rose to 45 mm. at the end of May, but steadily declined to 6 mm. by the last week of June. Throat cultures were persistently negative for Beta hemolytic streptococci. No parasites or ova could be recognized in the stool specimens on three separate occasions. Agglutinin titers for *S. dysentery* and *S. paradysentery* (W) could not be detected. The serum uric acid content was 4.9 mg. per 100 c.c.

The early roentgenographic examinations of the knees showed soft tissue swelling and a general haziness, but no erosions of the articular cortices; views of the left ankle indicated a mild bony atrophy. The cardiac silhouette failed to show any abnormalities. Intravenous pyelograms did not reveal any pathologic alterations.

During the last week of June the urinalysis disclosed normal elements chemically and microscopically. About 20 pounds of weight had been gained by mid-June and the fatigability and weakness were entirely overcome. The buccal lesions had entirely disappeared, the lingual areas of denudation had receded considerably, and lymph node enlargement was barely detectable. The consistency of the prostate was firmer. Subjectively and objectively the previously involved joints were normal; roentgenograms of the ankles and knees failed to disclose any periarticular swelling, haziness, articular changes, or bony atrophy. Clinically, cardiac abnormalities were at no time observed and serial teleroentgenograms remained normal.

Reëxamination on August 7 indicated that a gain of 30 pounds had been effected and that no clinical manifestations of the original disease were present except for a small superficial ulcer at the edge of the corona that measured .5 cm. in diameter. The urinary, hematologic, immunologic, cutaneous, cultural, prostatic, and stool tests were repeated with uniformly negative results. Scrapings from the small ulcer base, Kahn and Wassermann reactions were persistently negative and uninformative. The serial electrocardiograms showed the following changes in the P–R intervals (figure 1):

April 1, 1945	.22 sec.
April 15, 1945	.24
May 14, 1945	.24
May 22, 1945	.23
June 11, 1945	.24
June 25, 1945	.19
July 16, 1945	.22
August 10, 1945	.20

Case 2. A 23-year old white male was seen on November 12, 1944, for an urethral discharge and increased frequency of urination of two days' duration. He had been well until July 1944 when a paronychia of the right index finger required incision and drainage. In August 1944 an infection of the left external ear and a bursitis of the left shoulder had been successfully treated. On October 2, a cellulitis of the right calf necessitated incision and drainage.

The urethral and prostatic expressions contained numerous white blood cells but no organisms, and treatment was pursued in the form of daily prostatic massage. For the next two weeks a slight but constant terminal hematuria was observed. On December 2, 1944, photophobia, conjunctival congestion, and a mucopurulent discharge attended by bilateral iritis developed. He entered the hospital on December 4 with a temperature of 100.8° F. and a pulse rate of 98. Repeated smears of the urethral and prostatic fluids failed to show any organisms. Except for the urethral and conjunctival phenomena no other abnormal physical findings were encountered. On the second day of hospitalization the urethral discharge abruptly subsided after a seizure of lower abdominal pain that satisfactorily responded to the administration of enemata. Progressive swelling, limitation of motion, redness, heat and tenderness of the right wrist evolved during the first week while coincident vague pains of the left ankle were felt. Oral administration of sulfadiazine was begun immediately on December 6, one gram being given every four hours for 12 doses. This therapy was replaced by the instillation of penicillin solution into the conjunctival sacs every two hours. After 48 hours eight doses of intramuscular penicillin, 20,000 units at three-hour intervals were administered. A rhinitis appeared on December 11 that was quickly followed by congestion, vesiculation, and shallow ulcerations of the membranes of the tongue, gums, pharynx and cheeks. Anorexia, painful mastication, and painful deglutition were moderately severe. A second course of penicillin, 20,000 units every three hours, was initiated and maintained for one week during which time the oral manifestations disappeared. On December 18 frank inflammatory involvement of the left knee and ankle became evident and the signs enveloping the right wrist were intensified. A balanitis developed on January 1, 1945: the urethral orifice, the periurethral surface of the glans and the corona were covered with a brown crust resting upon a red base. Slow improvement of the eyes, joints, and genitalia followed but not until mid-February had all the phenomena vanished. On January 15 a bilateral axillary lymphadenitis prompted the administration of 20,000 units of penicillin every four hours for five days; the therapy was fortified by the application of hot compresses. The small amount of turbid fluid that drained through sinuses in the right axilla contained *Staphylococcus albus.* For the first 42 days the oral temperature fluctuated

between 99° and 101.8° F. Precordial pains were experienced at irregular intervals but never attended by objective clinical manifestations.

Diagnostic laboratory data could not be obtained. Smears and cultures of the eyes at the height of the infection revealed *Staphylococcus albus*. The urine was cloudy, the sediment loaded with white blood cells and clumps, and the test for albumin was 4 plus; 1 to 8 red blood cells were observed in the sediment under high-power fields on several occasions. These abnormal urinary elements disappeared on February 1. The white blood cell count on admission was 11,800 of which 84 per cent were polynuclear cells; the red cells and hemoglobin were normal; the non-protein nitrogen was 24, and the Westergren sedimentation rate was 40 mm. per hour. Until the latter part of January the leukocyte counts varied from 9,800 to 14,400 but thereafter normal values were obtained. Two blood cultures were made but remained sterile. Several Kahn and Wassermann tests proved to be negative. Roentgenographic visualization of the involved joints revealed a temporary mottled demineralization of the bones of the right wrist consistent with the conception of disuse atrophy. Pathologic states could not be identified in the cardiac silhouette, the lung fields, or flat abdominal plates.

In serial electrocardiographic tracings significant variations in the P–R intervals were measured. From January 23 to April 30, the duration of A–V conduction fluctuated between .18 second to .24 second (figure 2).

On May 17 the subject was transferred for further study. The cardiac findings were entirely negative except for an inconstant, localized, faint, systolic, apical murmur; the blood pressure was 134 mm. Hg systolic and 84 mm. diastolic. Palpable, shotty lymph nodes were found in both axillary and inguinal regions. The joints appeared normal, motion was unimpaired, and musculo-skeletal distress could not be elicited. The Westergren sedimentation rates failed to exceed 4 mm. per hour; the white blood cells varied between 6,400 and 7,100; the red blood cells and the hemoglobin determinations were normal. Blood cultures remained sterile; the serum uric acid content was 4.7 mg. per 100 c.c. Urine studies revealed no pathologic elements and only two or three white blood cells were counted under high-power fields; the urea clearance test was 110 per cent of average normal function; cultures of the urine sediment on different occasions developed isolated colonies of alpha hemolytic streptococcus, non-hemolytic *Staphylococcus albus*, and hemolytic *Staphylococcus aureus*. Intravenous pyelography resulted in adequate excretion of the dye and the shadows had normal outlines. The prostatic smears did not contain pus cells and cultures remained sterile. Beta hemolytic streptococci were not recovered from the throat. Wassermann and Kahn reactions were repeatedly negative. Agglutination for *B. abortus*, *S. dysentery* and *S. paradysentery* (W) could not be demonstrated. Stools failed to reveal any ova, parasites, or blood. Frei, brucellergin, PPD, and *H. ducrey* vaccine intracutaneous tests failed to evoke any skin reactions. Roentgenographic studies of the heart, the knees, the wrists and the ankles showed normal film patterns. On May 24 the EKG exhibited a P–R interval of .24 second and on June 4 an interval of .20 second. Thereafter until subject was last seen in August the duration of A–V conduction was persistently below .18 second (figure 2).

The P–R intervals varied as follows:

January 23, 1945	.20 sec.
February 1, 1945	.24
February 12, 1945	.21
February 23, 1945	.22
March 14, 1945	.18
March 23, 1945	.23
April 3, 1945	.20
April 30, 1945	.20

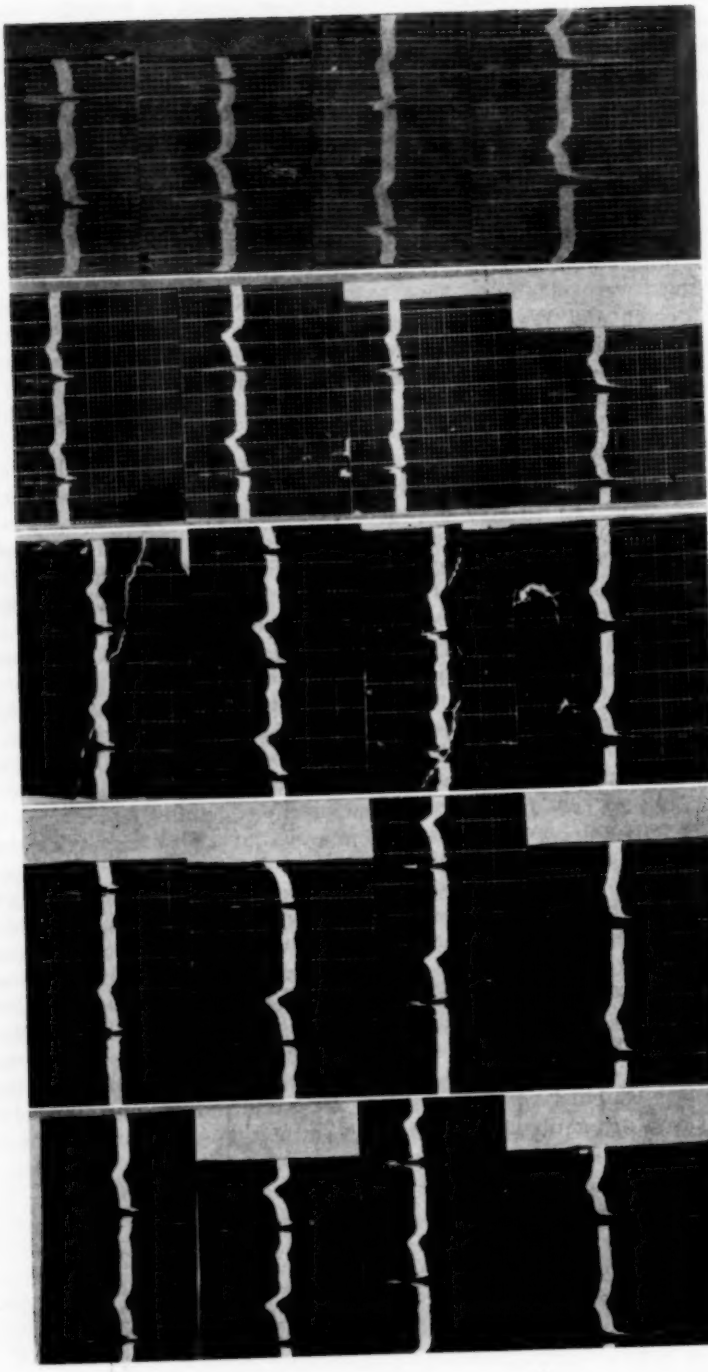

FIG. 2.

SUMMARY

Two cases of Reiter's disease are presented in which abnormal prolongations in auriculoventricular conduction appeared. In neither case could an infectious etiologic agent be found.

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INTOXICATION RESULTING FROM THE ADMINISTRATION OF MASSIVE DOSES OF VITAMIN D, With Report of Five Cases *

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The fact that massive doses of vitamin D may produce toxic symptoms and even death in man has been recognized for many years. It is only in the past few years, however, that the administration of this substance in massive doses has become popular with physicians and that the misinformation relative to its merits in the treatment of arthritis publicized by a certain widely read "digest" of current literature has induced some people to use it in self-medication. In the past year we have recognized the syndrome of vitamin D intoxication in five patients whose records are briefly reported later in this paper. Because these patients were very ill as a result of this intoxication, because the syndrome may easily be confused with other conditions, and because of the apparent increase in the number of these cases, it seems timely to discuss this subject.

In 1933 Rappaport and Reed [1] treated a number of cases of allergic conditions with massive doses of highly potent viosterol. They found that this substance raised the blood calcium to very high levels, lowered the potassium level, diminishing its wide fluctuations, and stabilized the calcium-potassium ratio at a relatively low level. Certain of the patients under treatment showed toxic injury and they found that the threshold of toxicity varied in different individuals and sometimes in the same person at different times. They felt that the toxic symptoms were easily recognized and that they abated promptly on discontinuance of the drug or reduction in the amount administered.

In 1934, Wyatt, Hicks, Allen and Thompson [2] reported the treatment of 40 cases of proliferative arthritis with vitamin D. They never administered over 300,000 international units per day and usually not over 200,000. They used irradiated ergosterol in sesame oil, viosterol, and vitamin D in propylene glycol. Twenty per cent of the patients had to discontinue this treatment because of toxic symptoms. They mention loss of appetite, drowsiness and slight headache as the more common symptoms, but in one of the eight cases showing toxic symptoms there occurred "violent persistent nausea, intense headache and sweating." They found that the calcium increase in the blood was from 0.75 to 0.95 mg. per 100 c.c. and that the calcium-phosphorus ratio was undisturbed.

In the same year Reed [3] reported on the symptoms of viosterol overdosage. He found that the first symptom of overdosage was frequency of

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urination. This symptom did not necessarily imply that the total output of urine was increased and it was not necessarily due to increased calcium excretion through the kidney. Urinary frequency was soon followed by nausea and vomiting and then, shortly, diarrhea. These symptoms abated in three to four days after the drug was stopped. Toxicity was always accompanied by loss of weight, which he felt was due to increased basal metabolic rate. The weight loss was accompanied by increased nitrogen excretion.

He states that toxicity is not synonymous with hypercalcemia. In comparing it with the effect of administration of parathyroid hormone he found that, with the hormone, a blood calcium level of 16 mg. per cent is dangerous, whereas with viosterol one subject had a blood calcium of 29 mg. per 100 c.c. of blood for two weeks without signs of toxicity and another maintained a level of 24 mg. for eight days with no toxic symptoms.

Reed concludes that one need not be apprehensive of doses up to 150,000 units per day for "indefinite periods," but it is interesting to note that Vrtiak and Lang,[4] reporting on the treatment of 20 cases of chronic arthritis, using from 150,000 to 250,000 international units per day, said that "Nausea developed in all patients; in a few, frequency of urination and nocturia."

In 1937 Steck, Deutsch, Reed and Struck [5] reported on their experimental studies regarding intoxication with vitamin D. This work was done on dogs. They point out that there is a species variation in susceptibility but that dogs and human beings are very much alike in this regard. The 64 dogs in their series received doses of vitamin D which would rarely, if ever, be approached in man. These doses ranged from one million units per kilogram per day down to less than 20,000 units per kg. per day. They all had marked elevation of blood calcium with a maximum of 21.6 milligrams per cent, marked weight loss and marked signs of intoxication. They all died in coma. The survival time with any dosage over 50,000 units per kg. per day averaged 12 days; with doses between twenty and fifty thousand units it averaged 39 days; and with less than 20,000 units, 68 days.

The objective symptoms were about the same as noted in the human subject, consisting of weakness and lassitude, anorexia, polydipsia, polyuria, psychic disturbances and diarrhea. Bloody feces were passed by 11 of the 64 dogs. In these, petechial hemorrhages were found in the mucosa of the stomach and intestines. In the most intense intoxications the premortal coma was a constant and characteristic feature. It was preceded by partial paralysis, slow shallow respirations, fine thready pulse, salivation and psychic changes whereby a previously tame and friendly dog was rendered unmanageable and vicious.

Autopsy was performed on each of these dogs. It was found that, of the 13 tissues selected for microscopic examination in each animal, the kidney proved to be the most vulnerable. Here, the first sign of damage was cellular degeneration. It was followed by the deposition of calcium in the damaged cells. There was great loss of fat, some of the animals being entirely devoid of it. These authors found that if the administration of the

drug was stopped early enough for the animal to survive, complete repair of the damaged tissues ensued, but that no animal or human being will recover so long as the medication is continued.

The increased excretion of calcium which takes place is not due to removal of the soft tissue deposits entirely, because it begins before there is any microscopic evidence of soft tissue deposits. It is thought to come from the trabeculae of the bone. The average level of calcium in the blood begins to fall after the output in the urine rises.

In addition to their experimental work, these authors collected data on the administration of vitamin D to 773 human cases. The dosage in these cases varied from 1,500 to 35,000 units per kilogram per day. A total of 63 cases, or 8 per cent, gave evidence of intoxication. Of these only two could certainly be said to have died of this intoxication.

They conclude that their experience indicates that "administration of massive doses of vitamin D should not be undertaken for any cause except under careful supervision of a physician who can and will carefully check the patient's condition at frequent intervals and who will see to it that the treatment is discontinued promptly on the appearance of the first signs suggestive of toxicity." They believe that any sign of kidney dysfunction is an absolute contraindication and that arteriosclerosis is probably a contraindication, therefore administration to older subjects should be undertaken "with extreme caution."

In this connection, Slocumb [6] concludes from his experience in the treatment of infectious arthritis that ". . . there is some risk of renal damage, which is temporary if the administration of vitamin D is discontinued promptly after evidence of toxicity appears, but serious damage may occur." He calls attention to the fact that concentration of urea in the blood may rise in some of these cases of intoxication.

From this brief review of part of the existent literature it appears that vitamin D in massive doses bears no relationship in its action to the use of this drug in deficiency disease. It is a powerful and dangerous drug which should be used with caution at all times, and there are definite contraindications to its use in some individuals. It mobilizes calcium from the trabeculae of the bones and thus raises the blood calcium level. The excess is excreted largely through the kidney. It often produces cellular degeneration in various organs of the body, and this is most marked and obvious in the kidney. The degenerated cells become the repository for calcium. The fat tissue of the body is rapidly burned up until it may practically disappear. Nitrogen may accumulate in the blood, presumably owing to the inability of the damaged kidney to excrete it. That it produces other chemical changes, all of which may not yet be known, is shown by its effect on the blood potassium which is lowered and loses its natural property of rapid and marked fluctuation. It is also apparent that mild intoxication with this drug is probably harmless unless it be permitted to continue over a long period of time and that complete restitution of the injured tissues usually takes place.

The symptoms of intoxication are readily recognized and have been enumerated above. If they are encountered during the course of the administration of the drug, the attending physician can recognize them promptly and act accordingly. However, if the patient is not closely observed, or if he is treating himself, as did some of our cases, the symptoms of intoxication may go on for considerable periods of time without recognition and may presumably cause permanent injury or even death.

Case Reports

Case 1. Mrs. E. A., white female, age 66, was treated for a chronic osteoarthritis involving numerous joints, and in increasing severity from 1933 to 1944. On Feb. 4, 1944, she came complaining of a great deal of pain from her arthritis. There was considerable tenderness over the spine, grating and limitation of motion of the knees, and tender, inflamed finger joints. The pulse rate was 84 and blood pressure 110 mm. Hg systolic and 70 mm. diastolic. Her general physical examination was not remarkable aside from the arthritic condition. On the day of examination she seemed to be less alert mentally than when last observed, but she seemed oriented and had travelled alone more than 50 miles to reach our offices.

Laboratory data on Feb. 4 revealed a normal urine with 1.023 specific gravity. The blood showed 12.5 gm. of hemoglobin with 4,160,000 red cells; 6,900 white cells and a normal blood picture. The sedimentation rate of the erythrocytes was 26 mm. in one hour. The blood Wassermann reaction was negative.

The patient expressed a desire to try massive doses of vitamin D, so she was given 50,000 unit capsules with instructions to begin with one daily and gradually increase to four capsules (200,000 units) daily. About two weeks later she complained of dizziness and stated that she had fallen several times. For this reason she was admitted to Lincoln General Hospital on March 13, 1944. She appeared apathetic and was disoriented. The general physical and neurological examination revealed nothing excepting a mild psychotic state and the old arthritic condition which had not improved under the vitamin D therapy. There was occasional incontinence of urine. The output per day could not be accurately measured but seemed to be increased. There was no nausea, vomiting or other gastrointestinal disturbance.

Laboratory data in the hospital showed a normal urine of specific gravity 1.025. The blood examination revealed 11.4 gm. of hemoglobin; 3,900,000 erythrocytes and 6,850 leukocytes per cu. mm. with a normal differential count. The urinary calcium was markedly increased and the blood calcium was 12.7 mg. per 100 c.c. of blood. The blood urea was 38 mg. per 100 c.c. One week later the urinary calcium was still increased. After two weeks without vitamin D the blood calcium had dropped to 11.8 mg. per 100 c.c. She was dismissed with but little change in the mild psychosis, but less tendency to ataxia upon standing and walking. We considered this to be a case of vitamin D intoxication with the somewhat unusual presenting symptoms of vertigo and tendency to fall and with at least an exaggeration of a tendency to senile psychosis.

Case 2. Mrs. J. B., a white female, age 54, was admitted to Lincoln General Hospital on Aug. 8, 1945 complaining of severe headache, nausea and vomiting of four weeks' duration with 16 pounds loss in weight. She had had painful and swollen joints, the knees, feet and hands being chiefly involved, for the past eight years. For this arthritic condition she had been taking vitamin D, 200,000 units daily for the first 30 days and 350,000 units daily for the next 60 days just preceding admission to the hospital. She stated that her arthritis had definitely improved. Physical examination showed nothing remarkable and no evidence of arthritis except some tenderness over the spine. Blood pressure was 160 mm. Hg systolic and 90 mm. diastolic.

Laboratory data on admission showed a urine of 1.012 specific gravity with albumin 2 plus and occasional hyaline and granular casts. The blood examination revealed a negative Wassermann reaction; a sedimentation rate of the erythrocytes of 23 mm. in one hour; 12 gm. of hemoglobin; 3,600,000 erythrocytes, 10,300 leukocytes per cu. mm., and a normal differential count. The blood urea was 80 mg. per cent, the blood creatinine was 3 mg. and blood calcium, 11.5 mg. per 100 c.c. of blood. One week later the blood urea had dropped to 50 mg. per 100 c.c. The urinary calcium was still increased.

At the time of discharge from the hospital she had no headache, her arthritis was in good condition, and her blood pressure was 180 mm. Hg systolic and 90 mm. diastolic. One month later there was a recurrence of the arthritis but there was no vomiting and only slight headache. Blood pressure was 180 mm. Hg systolic and 110 mm. diastolic. The urine showed a specific gravity of 1.012, only a trace of albumin and occasional hyaline casts and cylindroids. The blood urea at that time had dropped to 33 mg. per 100 c.c.

Case 3. Mrs. P. S., a white female, age 45, was admitted to the Lincoln General Hospital on Sept. 3, 1945 complaining of cramping pains in the legs for one week and a severe nocturnal headache for three days (previously she rarely had headaches). Because of a mildly painful joint in her right hand of two years' duration she had been taking 50,000 unit vitamin D capsules for the past year. She started with one capsule, then increased one capsule daily up to eight, then reduced one each day down to one capsule daily and then repeated the same cycle again and again. For the past six months she had thus taken an average daily dose of 225,000 units. There had not been any change in the very mild arthritis. Four months before admission she had some polydipsia and polyuria with a heavy sediment noted in the urine. These symptoms lasted for one month. This had recurred two months before admission with some burning on urination. Physical examination showed nothing remarkable excepting some redness and injection of the sclera. The only evidence of arthritis was slight tenderness of one interphalangeal joint. The blood pressure was 185 mm. Hg systolic and 105 mm. diastolic.

Laboratory data revealed a urine of 1.010 specific gravity containing albumin 1 plus but otherwise negative. The blood Wassermann reaction was negative. The sedimentation rate of the erythrocytes was 27 mm. in one hour. The blood contained 10.8 gm. of hemoglobin per 100 c.c., 3,930,000 red cells and 11,800 white cells per cu. mm. with a normal differential count. The blood urea was 61 mg. and blood calcium 13 mg. per 100 c.c. The phenolsulfonphthalein kidney function test returned 8 per cent of the dye in 15 minutes, 9 per cent the next 45 minutes, and 2 per cent the second hour, a total of 19 per cent in two hours.

About one week after discontinuance of vitamin D the patient looked and felt much better. The blood urea had dropped to 37 mg. per 100 c.c. The urea clearance was only 38 per cent of the normal and the specific gravity of the urine remained low. The blood pressure was 150 mm. Hg systolic and 90 mm. diastolic. About one month later the blood pressure was found to be 135 mm. Hg systolic and 85 mm. diastolic, she felt much better with only a slight morning headache and the scleral injection had entirely disappeared.

Case 4. Mrs. J. H., a white female, aged 68, had been treated for arteriosclerosis and hypertension for several years. Her blood pressure ranged from 166 mm. Hg systolic and 100 mm. diastolic to 208 mm. Hg systolic and 112 mm. diastolic. Following a sprained ankle and fracture of her right arm in 1944, she developed marked arthritis with stiffness, redness and swelling of her wrists, knees, ankles, hips and shoulders. In July 1945 she was given 50,000 unit vitamin D capsules with instructions to take one daily for one week, then to increase the dose to two capsules daily. She, however, continued to increase the dosage each week until in October she was

taking seven capsules daily (350,000 units). At that time she complained of vertigo, nausea and vomiting. The urine showed a specific gravity of 1.011, a moderate number of pus cells, many hyaline casts and cylindroids, and a few granular casts. The urinary calcium was slightly increased. Her blood pressure was the lowest ever recorded, 156 mm. Hg systolic and 90 mm. diastolic. The arthritis had improved somewhat.

Two weeks after all vitamin D had been discontinued she felt much better, the appetite was good and there was very little vertigo. The urinary calcium was not increased and the blood urea was 20 mg. per 100 c.c. of blood.

Case 5. Mr. M. G., a white male, age 29, had tuberculosis of the spine when five years of age with a marked dorsal kyphosis. When 24 years of age he had a cold abscess in the back and left thigh. The present illness dated back two weeks when he vomited for several days which was very unusual for him. He was again vomiting when first seen on March 6, 1945 and had lost about 10 pounds in weight. He stated that four months before he had had some back and sciatic pain which had improved upon receiving some vitamin B injections which he had continued to take occasionally since that time. He said that he was taking no other medicine. Physical examination was essentially negative except for the severe dorsal kyphosis which reduced the longitudinal diameter of the abdomen by about 50 per cent. The blood pressure was 126 mm. Hg systolic and 94 mm. diastolic.

Laboratory data revealed a negative Wassermann reaction, a sedimentation rate of 20 mm. in 1 hour, 13 gm. of hemoglobin per 100 c.c. of blood, 4,710,000 erythrocytes, 7,050 leukocytes per cu. mm. and a normal blood picture. The urine had a specific gravity of 1.011 with a few leukocytes. In rechecking the urine on the same day, many cylindroids were found. During the next few weeks, repeated urine examinations showed a trace of albumin, many hyaline casts and cylindroids and occasional granular casts. The phenolsulfonphthalein test returned 16 per cent of the dye in 15 min., 12.5 per cent in the next 45 min. and 12.2 per cent in the second hour, a total of 40.7 per cent. The blood urea was 66 mg. per cent. Roentgen-ray examination of the gastrointestinal tract was negative.

After several days of vomiting he again felt fine for two weeks, when the nausea and vomiting recurred. This same cycle recurred for the third time when it was discovered that he had been taking from one to eight 50,000 unit capsules of vitamin D daily for the past four months. When he vomited, he had to stop the vitamin D but would take it again as soon as he could eat. The urine was then examined for calcium which was not found to be increased, but the blood calcium was 12.5 mg. per 100 c.c.

After stopping the vitamin D, his appetite was again good and he felt well. After 20 days the blood calcium was down to 10.6 mg. and the blood urea, to 49 mg. per 100 c.c. Two weeks later (over one month after stopping the ingestion of vitamin D) the urine showed no albumin, no increase in calcium, and only a few hyaline casts and cylindroids; but the blood urea had again risen to 60 mg. with a hemoglobin of 8 gm. per 100 c.c. of blood.

It seems probable that the kidney damage was severe enough so that full restitution may be impossible and secondary hypochromic anemia has developed.

The treatment in all of these cases consisted of:

1. Discontinuing the administration of vitamin D.
2. Forcing fluid intake.
3. Administration of vitamin B in large doses—usually by parenteral injection.
4. A restricted protein diet for a short time in some cases.

Discussion

In four of five of these cases ranging in age from 29 to 68 years vitamin D was taken in dosage larger than is considered safe, namely 150,000 units per day. Two of the five cases were victims of arteriosclerosis and hypertension, conditions which have been said to contraindicate the use of this drug. In two cases the dosage was increased voluntarily by the patient much beyond the amount ordered by the physician. In case 1 the mental status of the patient, while not obviously psychotic, was known to have deteriorated in comparison with previous observations. At our last observation the psychosis was obviously worse than before taking vitamin D. Although this condition has not been mentioned as a contraindication to massive doses of vitamin D, the moderate dosage she received, 200,000 units per day, seems to have increased her psychic disorder. This effect has been noted in dogs as stated earlier in this paper. It is possible that psychic disorders, especially in the aged, should be considered as a contraindication to the use of this substance in massive dosage.

The most common symptoms were nausea, vomiting and headache. Associated with these symptoms there was a group of findings indicating renal injury and consisting of albuminuria of moderate grade, the presence of granular casts, an elevation of blood urea and a depression in the output of phenolsulfonphthalein.

Blood calcium was slightly increased in the four cases in whom it was estimated and there was generally an increase in urinary calcium but this was noted as marked in only one instance.

A moderate normochromic anemia was found in three of the five cases and slight leukocytosis, in two.

Conclusions

1. Vitamin D in massive doses is a toxic substance which produces parenchymal injury especially in the kidney.
2. In doses greater than 150,000 units per day, it is a dangerous drug.
3. In individuals who have evidence of renal disease it should not be used.
4. In those with hypertension and signs of arteriosclerosis and those who show any signs of psychic disturbance its safe use is open to question.
5. In any individual the use of this substance should be frequently and carefully supervised. The discontinuance of the drug at the first sign of intoxication will usually cause the prompt disappearance of symptoms and, probably, the restitution of the injured tissues.
6. Injury to parenchymatous organs, especially the kidney, may progress to the point where restitution is impossible, as seems to be true in our case 5.

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CASE REPORTS

FRIEDLÄNDER PNEUMONIA TREATED WITH STREPTOMYCIN; REPORT OF A CASE WITH PROMPT RECOVERY *

By NORMAN LEARNER, Captain, and WILLIAM R. MINNICH, Captain, M.C., A.U.S., F.A.C.P.

THE introduction of streptomycin has provided a new antibiotic effective against many Gram negative organisms unaffected by penicillin. The Friedländer bacillus (*Klebsiella pneumoniae*) has been shown to be susceptible to streptomycin in vitro,[1] but the effect of this agent on acute Friedländer pneumonia is not known.† Recently, the opportunity arose for just such a therapeutic trial. The patient responded so rapidly to streptomycin that a report was felt justified, especially since this type of pneumonia is so refractory to other drugs.

CASE REPORT

The patient, a 36 year old white infantry soldier, sustained a penetrating shell fragment wound of the right forearm on December 15, 1944, in France. Three days after injury the fingers of the right hand began to turn black. Dorsal sympathetic blocks were performed, but by the tenth day the fingers were completely black. He was then evacuated through channels to the zone of the interior. The soldier complained of severe pain in the arm and forearm, and on February 19, 1945 a dorsal sympathectomy was performed with immediate relief of much of the discomfort in the extremity. The forearm wound continued to drain, and culture obtained on February 26, 1945 disclosed "bacilli of the mucosus encapsulatus group." A later culture on March 17 disclosed only *B. subtilis* and *B. proteus*. On March 2 the gangrenous portion of the fingers was removed. He subsequently developed an abscess of the right hand which was drained on May 29, 1945. On July 26, 1945 he was transferred to this plastic surgery center and on arrival the forearm wound was healed, but slight drainage persisted in the amputated stump of the right index finger. During the period from February until May 1945, he received penicillin, 20,000 units intramuscularly every three hours, almost continuously.

On October 3, 1945 a revision of the stumps of the right index and middle fingers was performed under general inhalation anesthesia. On October 8 the middle finger stump was practically healed, and the index finger stump was healing satisfactorily. The surgeon stated that there was no active infection. On the evening of October 10 he developed sharp pain in the lower left chest posteriorly and in the left axilla. Examination of the chest at that time showed nothing remarkable and there was no fever. However, the next day the pain persisted and temperature rose to 100° F. A slight unproductive cough appeared. On October 12 a medical consultation was requested.

* Received for publication May 23, 1946.

† At the time this report was submitted we were not familiar with the paper of HERRELL, W. E., and NICHOLS, D. R.: The clinical use of streptomycin: A study of 45 cases, Proc. Staff Meetings, Mayo Clin., 1945, xx, 449, in which the authors described two cases of Friedländer pneumonia treated with streptomycin.

On examination the patient was obviously uncomfortable, although he did not appear seriously ill. Motion of the left chest was markedly restricted. The percussion note was dull at the left base and low in the left axilla. Breath sounds were diminished in these areas, but no râles were audible. A coarse friction rub was present just below and medial to the left scapular angle. It was felt that the patient had an early left lower lobe pneumonia, although the possibility of pulmonary infarction was entertained because of a history of thrombophlebitis in the right leg one year previous with a minor recurrence in August 1945. Chest roentgenogram on October 12 disclosed a faint area of consolidation in the axillary portion of the left lower lobe with slight elevation of the left diaphragm. The left costophrenic angle was slightly hazy, but no free fluid appeared to be present. Blood count disclosed 10,550 leukocytes of which 71 per cent were polymorphonuclear neutrophiles. Sputum cultures was obtained, and penicillin therapy was instituted on October 12 (40,000 units intramuscularly every three hours).

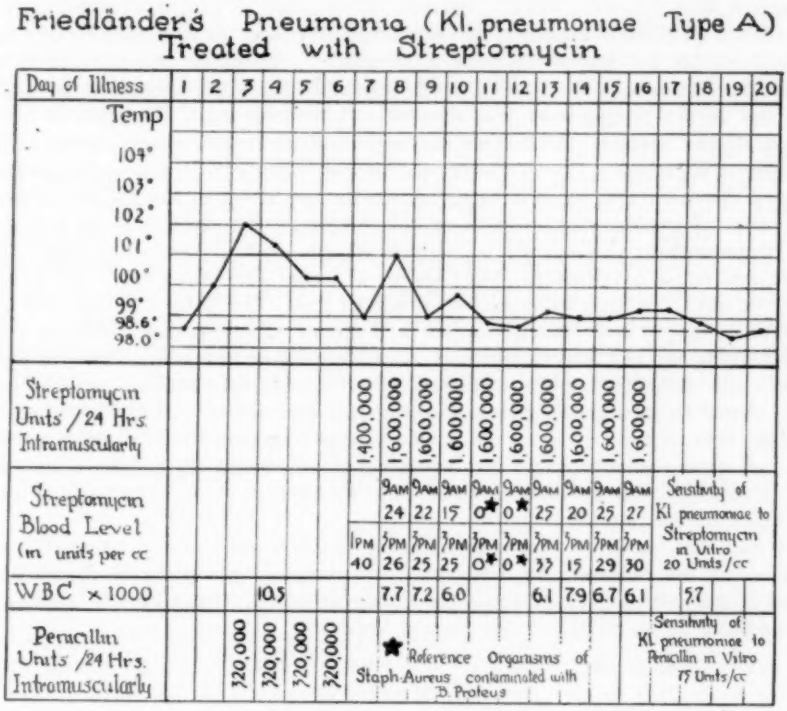

FIG. 1.

Because of the severe pleuritic pain, the left chest was strapped with adhesive. On October 13 there was no change in the patient's condition. He continued to complain of severe pain in the left axilla and the physical signs were the same. On October 14 his fever had fallen somewhat and he began to cough up small quantities of tenacious, frankly bloody, sputum. Examination of the chest disclosed a greater area of dullness at the left base and in the left axilla. A second roentgenogram on October 15 showed increase in the consolidation. The lateral portion of the involved lower lobe appeared very dense while the medial portion showed only mottled density. Also noted was moderate pleural thickening over the right apex. Sputum culture report on October 15 was "Friedländer bacillus (*Kl. pneumoniae* type A), 4 plus." Neufeld

typing for pneumococci was negative. On October 16 the patient still appeared acutely, but not seriously, ill. The signs of consolidation were more extensive over the left lower lobe. There was increased vocal resonance over the involved area but the breath sounds were still diminished. Despite the fact that the temperature was falling the patient was clinically worse. It was decided to institute streptomycin therapy since reports indicate that Friedländer bacillus is insusceptible to penicillin.[2] Accordingly, at noon on October 16 penicillin was discontinued and streptomycin begun in doses of 200,000 units intramuscularly every three hours. A second sputum culture, obtained just before this change in therapy, again revealed Friedländer bacillus (*Kl. pneumoniae* type A) 4 plus. The sensitivity of this organism to streptomycin was determined and found to be 20 units/c.c. of an F.D.A. broth culture. Streptomycin blood levels were determined at 9 a.m. and 3 p.m. daily by the method of Stebbins and Robinson.[3] Unfortunately a blood culture was not obtained until about 18 hours after streptomycin therapy was begun, and this was negative. The patient made rapid improvement, and sputum cultures obtained on October 17 and daily thereafter were negative for Friedländer bacillus. He continued to cough up tenacious bloody sputum for three days, but by October 18 there was return of resonance and increase in breath sounds at the left base. The hand wounds appeared clean and there was no drainage. By October 20 the temperature was normal and remained so. The patient tolerated the streptomycin well and there were no untoward reactions, except soreness locally at the site of injection. Chest roentgenogram on October 21 disclosed considerable clearing in the density at the left base. A shadow persisted in the axillary portion of the left lung. Near the superior and medial margin of this shadow there was a small area of translucency which could possibly represent a small cavity, although the appearance was not at all definite. On October 25, after the temperature had been normal for six days, the streptomycin was discontinued. The patient then made an uneventful recovery. Chest roentgenogram on October 31 revealed still further clearing of the density in the left lower lung field. The left diaphragm was in normal position, but there were definite diaphragmatic adhesions in the mid-portion producing some tenting. Another roentgenogram on November 9 showed only slight haziness in the axillary portion of the left lower lung field and persistence of the diaphragmatic adhesions. A final roentgenogram on November 21 disclosed no residual parenchymal lesion. The left diaphragm was elevated and there was evidence of pleural thickening in the region of the interlobar fissure.

The fact that bacilli of the mucosus encapsulatus group were recovered from the forearm wound on February 26, 1945, was unfortunately not discovered until the patient had completely recovered from the pneumonia. By this time all wounds were well healed and no material for culture was available.

Comment

The Friedländer bacillus (*Kl. pneumoniae*) is the etiologic agent in a small but definite percentage of lobar pneumonia cases. Julianelle[4] described three serologic types, A, B, and C, and a mixture X, type specificity depending on capsular polysaccharide. Type A was the responsible agent in 74 per cent of one series of 45 cases of Friedländer pneumonia.[4] The disease may lead to early death, recovery in a relatively small percentage, or chronic suppurative pulmonary disease with abscess formation. The mortality is high. Solomon[5] reported deaths in 97 per cent of 32 cases receiving no chemotherapy. Perlman and Bullowa[6] found that sulfanilamide, sulfapyridine, or type specific serum, or combinations of these were of little value. Hyde and Hyde[7] state that the value of chemotherapy is not clear, but that sulfonamides are of some value in human

Friedländer pneumonia in the early stages. Anderson,[2] in a review of penicillin therapy, lists the Friedländer bacillus among a group of organisms that are not adversely affected by concentrations of penicillin that can be achieved in the blood or tissues. He points out, however, that several relatively insusceptible organisms can be inhibited in vitro by use of relatively high concentrations of penicillin, indicating that penicillin insensitivity is a relative quality. This is demonstrated in the case here reported. Penicillin sensitivity studies in vitro disclosed that a concentration of 75 units of penicillin per c.c. was necessary to inhibit the growth of this strain of *Kl. pneumoniae*. Levels approaching this are never approximated in penicillin therapy. It can be argued that such levels are not necessary in vivo, since the action of penicillin in human infections is bacteriostatic—that the actual destruction and elimination of the infecting organisms are probably effected by the normal defense mechanisms of the host.[2] We thought this at first to be the case in our patient, since his temperature began to fall while he was receiving penicillin. However, since there was spread of the pneumonic process, and since the sputum cultures still showed the presence of the organisms, streptomycin therapy was decided on. The response was prompt, and the sputum cultures were consistently negative after two days of treatment. It is of interest that sensitivity studies in vitro disclosed 20 units of streptomycin per c.c. of F.D.A. broth culture to inhibit this strain of *Kl. pneumoniae*, and that such levels were attained in the blood by the dosage of streptomycin employed.

An unusual feature in this case was the presence of "bacilli of the mucosus encapsulatus group" (probably *Kl. pneumoniae*) in the culture of the forearm wound on February 26, 1945. Since there were small draining areas in the finger stumps at the time of the plastic procedure on October 3, 1945, it appears most likely that Friedländer bacilli were present in the wounds of the hand, and that the operation resulted in low grade bacteremia culminating in the pneumonia. Unfortunately, a blood culture was not obtained until 18 hours after the institution of streptomycin and this was negative.

Summary

A case of Friedländer pneumonia caused by *Kl. pneumoniae* type A is described, which was successfully treated with streptomycin after apparent failure of penicillin. It is appreciated that the treatment of a single case does not establish the value of a new therapeutic agent. However, the rapid recovery from a disease ordinarily so refractory to other known methods of treatment should indicate the further trial of streptomycin in Friedländer pneumonia.

We are grateful to Lieutenant F. V. Lucas, Sanitary Corps, Army of the United States, for the bacteriologic studies including sensitivity determinations and streptomycin levels.

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HEMATOPORPHYRINURIA: REVIEW OF LITERATURE AND REPORT OF A CASE OF CHRONIC TYPE*

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PORPHYRINS are chemical compounds participating in the normal pigment metabolism and occurring throughout the plant and animal worlds. They are of special interest in medicine because of their occurrence in hemoglobin, in bile-pigments, in chlorophyll, and in the widely distributed coloring matter, cytochrome. All porphyrins have a common chemical structure, namely four pyrrole rings bound by four additional carbon atoms, and are able to form compounds with metals. In the blood pigment the porphyrin is called protoporphyrin and this combined with iron and the protein fraction, globin, forms the basis for hemoglobin.

The organism receives the porphyrin either directly or by transformation of the chlorophyll, the hemoglobin, or the myoglobin in the gastrointestinal tract. This transformation probably takes place through the action of intestinal bacteria. Part of the porphyrin is absorbed by the intestine and conducted to the liver where it is changed to bilirubin or to other forms of porphyrin; part of it enters the circulation and is carried either to the organs of storage or to the kidneys where it is excreted. In addition to this, production of porphyrin takes place in the reticulo-endothelial system, especially in the liver cells, during the course of the transformation of hemoglobin to bilirubin, and it also takes place in the bone marrow during the synthesis of the blood pigment. Pathologic porphyrinuria may therefore be the result of disturbances in any of the organs participating in the pigment metabolism.

Two porphyrins appear to be the most important in cases of pathologic porphyrinuria, namely, (1) coproporphyrin which occurs in normal feces, and (2) uroporphyrin which is found in small quantities in normal urine. These two porphyrins, as they occur normally in excreta, are probably derived from plant and animal tissues taken as food. In certain pathological conditions both uroporphyrin and coproporphyrin are produced in excess in a manner as yet unknown and excreted in the urine and feces. Günther,[6] who did the pioneer work in this field, believed that the disease represents a constitutional anomaly of pigment metabolism in the form of a reversion to an embryonic type. This he based on the fact that the embryo's red cells contain uroporphyrin as well as hemoglobin

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From the Medical Service of the Wesson Memorial Hospital.

and that thus far no satisfactory evidence has been found that these porphyrins are derived from the breakdown of hemoglobin. Subsequent investigations, especially those indicating that porphyrias are a familial disease, tended to confirm Günther's original idea that the disease is caused by an inborn error of porphyrin metabolism.

From the etiologic point of view the porphyrias have been classified into congenital, acute, and chronic forms. The acute form has been further subdivided into acute toxic and acute idiopathic porphyria.[1, 9] In regard to the acute toxic and the acute idiopathic forms, Watson and others [11, 8] pointed out that these two forms probably represent the same condition and that they are indistinguishable either clinically or by laboratory procedures. The acute toxic form of porphyria is recognized only by the demonstration of a toxic agent, usually a barbiturate or a sulfonamide, which apparently are etiologic factors.[3] Anxiety, exhaustion and infection are also given by some authors, notably Eldahl,[2] as precipitating factors for the acute toxic form. On the other hand, the acute idiopathic porphyria, it is assumed, is also produced by some toxic agent, which has not been identified.

Clinically the congenital form, which is rare and inherited as a recessive Mendelian characteristic, is featured by (1) the color of the urine, (2) the pigmentation of the teeth and bones, and (3) the sensitivity of the skin to light. The urine varies from a pink to a red or black color and often darkens after exposure to light (so-called photo-oxidation). The porphyrins found in the urine are coproporphyrin and uroporphyrin. There is a brown to pink pigmentation of the enamel of the teeth, and the bones of the hand may develop a brown pigmentation which may become so deep that it is visible upon transillumination. The skin lesions, which vary from simple erythema to vesicle formation and large bullae filled with a colorless or blood-stained fluid, are caused by the sensitivity of the skin to ultraviolet light. This skin sensitivity is usually evident in childhood and affects mainly the hands, neck and face. Healing leaves permanent scars and in some cases a brownish pigmentation of the original lesions. Although the condition continues through life and can be warded off as long as precaution against excessive sunlight is taken, Garrod [4] thinks that the prognosis must be guarded since in these cases there is a great tendency toward the development of a very fulminating type of pulmonary tuberculosis.

Both the acute toxic and the acute idiopathic forms of porphyria are more common in women than in men.[5] The condition may be familial and then is inherited as a dominant Mendelian characteristic. In women, according to Günther,[6] it is very often associated with menstrual disorders. The symptoms of acute porphyria of either type include, (1) the voiding of red urine (port wine color) or brownish urine which may become red after exposure to light, (2) various types of gastrointestinal disturbances and abdominal pain, such as nausea, constipation, vomiting, (3) various abnormalities of the nervous system, as evidenced by psychotic manifestations or paralysis, usually of the ascending (Landry) type, (4) jaundice, (5) renal damage and (6) very rarely pigmentation of the skin or dermal photosensitivity. During the attack the urine usually contains a mixture of coproporphyrin and uroporphyrin. The central nervous system involvement and the psychic disturbances usually occur only in the acute toxic form, and if these symptoms are present, the prognosis is considered very poor, the mortality rate in these cases being about 75 per cent. The leading symptoms

in the acute idiopathic form are intermittent attacks of voiding port-wine colored urine. These attacks last from one to three weeks, and then the porphyrin usually disappears from the urine until the onset of a subsequent attack. In these cases there is often evidence of hepatic dysfunction, such as positive urinary reactions for urobilin and urobilinogen and intermittent attacks of mild jaundice. The pathologic changes in the fatal cases are chiefly in the nervous system and consist of degenerative changes in the peripheral nerves, the spinal cord, and the ganglia of the autonomic nervous system, especially those of the abdominal viscera. Presumably, the latter changes are responsible for the abdominal symptoms.

The chronic form contains those cases which do not fall into the two previous groups. This type runs a more protracted course and may have acute exacerbations, during which there usually is a heavy urinary excretion of porphyrin, which gives the urine a dark color. Usually the gastrointestinal symptoms, such as cramps, vomiting and constipation predominate, and frequently there is light sensitivity, though not as pronounced as in the congenital group. Nervous depression has also been observed occasionally. The chronic form may follow the prolonged use of barbiturates, especially sulfonal, trional, and veronal, even in ordinary dosage. Prognosis is somewhat better in this group than in the acute toxic group, but recovery is usually slow, and in rare instances this type has also proved to be fatal.

The diagnosis of porphyrinuria of any type depends upon the history, the clinical picture and the laboratory data, especially the examination of the urine. It is of great importance to recognize and confirm this condition because failure to do so, according to Geissler,[5] "often misled to surgical interventions, because a diagnosis of intestinal obstruction, peptic ulcer, gallstone disease, renal calculi or appendicitis was made. Also hysteria or malingering has been assumed on account of negative organic findings." In the urine, the demonstration of uroporphyrin by spectroscopic examination is pathognomonic for this disorder. According to Nesbitt and Watkins[9] patients with acute porphyrinuria usually excrete uroporphyrins III and I in the urine with a great predominance of the type III isomer, and only small amounts of coproporphyrin III and no uroporphyrin in the feces. Occasionally great difficulties may be encountered in demonstrating the characteristic spectroscopic bands of uroporphyrin, because this substance may be excreted as a metal complex. This difficulty, however, can be overcome by first treating the urine with acid. Another diagnostic test of value is the exposure of the urine to filtered ultraviolet rays. A pink fluorescence develops if porphyrins are present.[1]

As far as the treatment of the porphyrias is concerned, nothing of a specific character has been found, since the cause of the disorder still remains unknown. Among therapeutic measures which prevent the excretion of porphyrins, liver extract and vitamins B and C have been mentioned with varying results.[7, 10] The intravenous use of calcium has also been reported as improving the manifestations of the acute porphyrias.[1] In the congenital type exposure to sunlight should be avoided and the skin lesions be protected from secondary infections, while in the chronic type the offending agents, such as barbiturates and sulfonamides should be discontinued. The same naturally holds true for the acute toxic type, where the offending agent should be eliminated at once. Otherwise the treatment is purely symptomatic and supportive.

The following case is reported because of the diagnostic difficulties it presented. The failure to recognize this condition led to several major surgical operations and at one time to the somewhat vague diagnosis of psychoneurosis.

Case Report

The patient, a 37 year old American-born housewife, was admitted to the hospital because of repeated attacks of voiding dark red urine, abdominal pain followed by diarrhea, nervousness and a slight yellowish tint of her skin.

She had had intermittent attacks of voiding red urine for the preceding 14 years and had consulted several physicians. The present admission was her fifth to a hospital. The first admission to a hospital was 14 years previously when she was treated for pyelitis and essential hematuria. At that time she also had intermittent abdominal pain, which was thought to be due to a chronic appendicitis. For this reason an appendectomy was performed. However, her abdominal pains as well as the attacks of voiding red urine persisted, and two years later she again was operated on, this time for a cystic right ovary which was believed to be the source of her abdominal pains. Following this, the abdominal pains disappeared for a while, but the attacks of voiding red urine persisted. These attacks occurred about two or three times a year and lasted for about one week. During these attacks there was a history of frequency, dysuria and nocturia, which were not present during the free intervals. Just prior to these attacks, it was noticed that the patient became very nervous and depressed. She also had slight abdominal pain, nausea and diarrhea during the attacks. Five years following her second hospital admission she was again admitted because of the increasing frequency of these attacks which were now accompanied by low back pain. At that time a complete and thorough genito-urinary study was performed, which included both retrograde and intravenous pyelograms. The urine examinations were entirely negative, no red blood cells being present in spite of the red color of the urine. Guinea pig inoculations with the urine proved to be negative for tuberculosis. The retrograde and intravenous pyelograms were normal and chest roentgenogram was negative for tuberculosis. The possibility of hyperthyroidism was also considered at that time, but the basal metabolic rate was within normal limits. However, following her discharge from the hospital, the attacks of voiding red urine continued and it was noted that her depressed mental states, as well as the attacks of abdominal pain, increased both in frequency and in severity. At that time, too, her skin started to become slightly yellowish in color. Because of that she again entered the hospital two years later, and this time a right nephrectomy was performed. The pathologic report of the removed kidney both macroscopically and microscopically was entirely negative. After her recovery and discharge from the hospital, she again started to void red urine and the yellowish tint of her skin increased gradually but steadily and finally reached a point where there was frank clinical jaundice present. At the same time her abdominal symptoms continued and there also was some tenderness in the upper right quadrant. She was not able to retain any food. There also was diarrhea. These symptoms persisted and the attacks of voiding red urine recurred at three to four month intervals. Because of jaundice and the abdominal symptoms she again entered the hospital where a cholecystectomy was performed. However, the pathologic examination of the gall-bladder was negative and no stones were found. She made a good recovery from the operation but her abdominal symptoms, such as diarrhea, nausea and vomiting, as well as the slight icteric color of her skin and the attacks of voiding red urine coupled with a depressed mental state persisted, so that at one time, since no objective organic findings could be detected, a diagnosis of psychoneurosis was made. All these symptoms continued until her present admission.

At no time during her long illness was there any history of prolonged or excessive

use of barbiturates or sulfonamides, she did not have any skin discolorations except jaundice, and there also was no evidence of any dermal photosensitivity. The menstrual history revealed that she had always had severe dysmenorrhea and that she already was experiencing menopausal symptoms before her oöphorectomy. She had been married for 18 years but never became pregnant.

The only pertinent factor in the family history was that patient's father died at the age of 66 years of "kidney trouble," the exact nature of which she was unable to recall. However, patient stated that her father prior to his death had similar attacks of voiding dark red urine. These attacks lasted for a few weeks and then disappeared spontaneously.

Physical examination on present admission revealed an underdeveloped and somewhat undernourished white female of the asthenic type. She appeared very restless, apprehensive and somewhat depressed mentally. The skin showed a slight icteric tint, and the mucous membranes were somewhat pale. No enlarged lymph nodes were palpable, and the thyroid gland appeared to be normal. Heart and lungs were normal. There was rather diffuse tenderness of the abdomen, with some localization over the right upper quadrant. The liver was enlarged and palpable three fingers'-breadth below the right costal margin. The liver was soft but tender on palpation. The neurologic examination was entirely negative. Blood pressure was 110 mm. Hg systolic and 70 mm. diastolic.

The laboratory examinations were as follows: The urine was dark red in color with specific gravity ranging between 1.018 and 1.026. It contained some granular casts, bacteria and a few pus cells. No red cells nor hemoglobin were detected in any of the urine specimens. The red blood cell count varied between 3,790,000 and 5,130,000 with the hemoglobin values between 80 per cent and 95 per cent (Sahli method). White cell count was between 6,500 and 7,700 with a normal differential count. Examination of the blood smear showed nothing of significance. Wassermann and Hinton tests were negative. The sedimentation rate was 12 mm. in one hour (Wintrobe method). Blood culture and culture of the urine showed no growth, and guinea pig inoculation of urine was negative for tuberculosis. The fasting blood sugar was 96 mg. and the non-protein nitrogen was 30.5 mg. per 100 c.c. The Quick prothrombin time was 22 seconds. Stool examination was negative for occult blood. The concentration of proteins was 6.5 gm. per 100 c.c. of serum, the albumin being 4.0 and the globulin 2.5. Roentgenograms of the chest were negative, and the basal metabolic rate was minus 4 per cent.

The port-wine color of the urine deepened on exposure to light, and the characteristic fluorescence of porphyrinuria was observed when the urine was placed under ultraviolet light and was even noticeable when a test tube of urine was viewed in direct sunlight. Spectroscopic examination of the urine showed the characteristic absorption bands for uroporphyrin as the zinc metal complex.

Her clinical course while in the hospital was characterized by several episodes as previously described during which times her urine, otherwise normal in appearance, became dark brown or reddish-brown in color. Abdominal symptoms such as nausea, vomiting and diarrhea were also present, and at times there was diffuse tenderness over the entire abdomen. The jaundice varied from a very minimal degree to frank clinical icterus. There also was excessive sweating, mainly at night. There was no fever at any time.

Treatment in this case consisted of general supportive measures and specifically of plasma and whole blood transfusions, following which the attacks of voiding red urine seemed to stop momentarily, but only to return again later. She was also given both vitamin B and vitamin C in large doses intramuscularly and by mouth, but this too seemed to have only slight temporary effect on her condition and the attacks of voiding red urine as well as the abdominal symptoms recurred at intervals.

SUMMARY AND CONCLUSIONS

A case of chronic porphyria has been described in which the diagnosis was confirmed by the demonstration of uroporphyrin in the urine and by spectroscopic examination.

The clinical picture in this case was characterized by attacks of voiding dark red urine (port wine color) and various types of gastrointestinal disturbances, jaundice, menstrual disturbances and mild mental depressions.

The treatment consisted of plasma and whole blood transfusions and large doses of vitamin B and vitamin C, all of which seemed to have but temporary effect on the condition.

This case is of special interest because the failure to recognize this condition in the incipient stage led to several false diagnoses with subsequent unnecessary surgical operations, all of which failed to control, improve or cure the condition.

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HODGKIN'S DISEASE INVOLVING THE PITUITARY GLAND WITH DIABETES INSIPIDUS *

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HODGKIN'S granuloma is a fairly common entity, but involvement of the pituitary gland with symptoms is rarely encountered. In a survey of the literature, only four cases of lymphogranuloma of the hypophysis were found, one case

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without symptoms and the other three showing the symptoms of diabetes insipidus. A case of the later type is described.

Case Report

The patient, M. C. S., was a white male, aged 47, a farmer, admitted March 24, 1945. The family history and the past history presented nothing of significance. The patient had been in good health until August 1944 when he first noticed the appearance

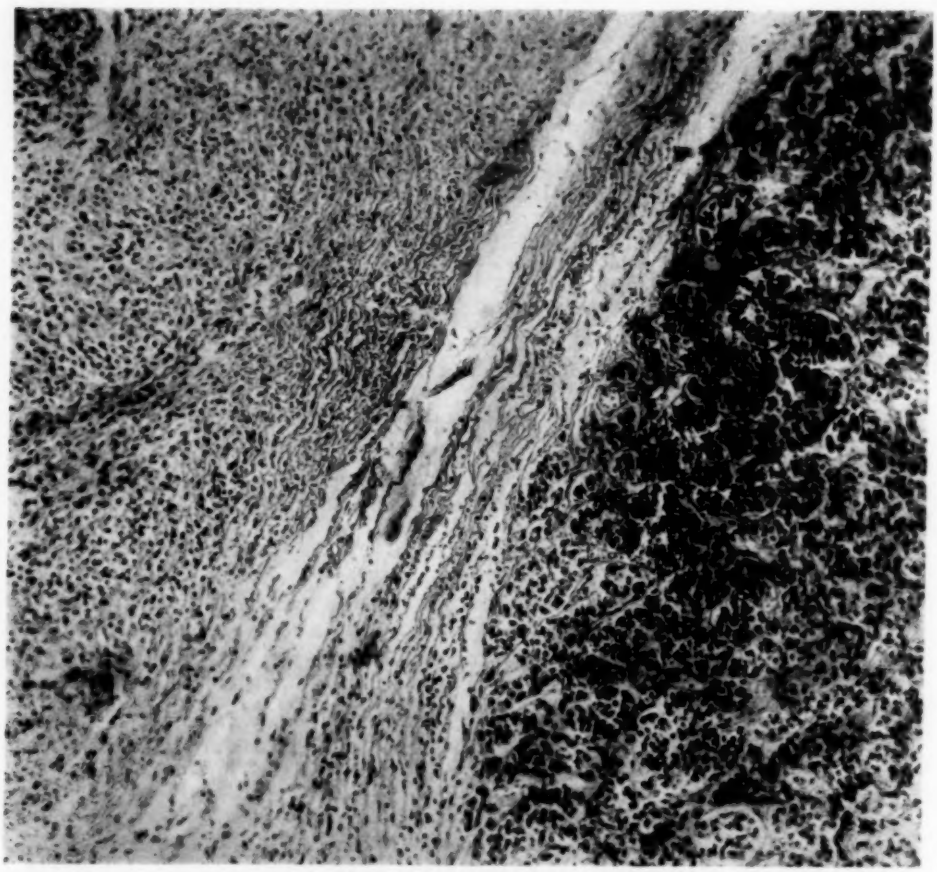

Fig. 1. Low power photomicrograph of a section through the anterior and posterior lobes of the hypophysis, showing round cell infiltration and multinucleated giant cells along with an increase in fibrous stroma. × 100.

of "lumps" on the left side of the neck. These gradually increased in size but caused him no particular discomfort. Later, he noticed smaller masses on the right side of his neck, axilla and groin. He stated that he had lost a great deal of weight.

Since February 1945, the patient had developed a progressively increasing weakness and a severe thirst. He stated that he drank about three gallons of water daily and urinated an almost equal quantity. He did not notice any polyphagia associated with the polydipsia and polyuria.

Physical examination disclosed bilateral enlargement of lymph nodes in the neck, axillary and inguinal regions. The nodes varied in size from 1 cm. to 3 cm. in diameter. They were firm and some appeared to be coalesced, but most of them were discrete. Palpation of the nodes showed mild tenderness on pressure. The skin was dry and loose. The patient had a temperature of 103° F. on admission.

Radiographs of the chest revealed pulmonary emphysema. No mediastinal enlargement was seen. Radiographs of the skull revealed a normal sella turcica and normal anterior and posterior clinoid processes.

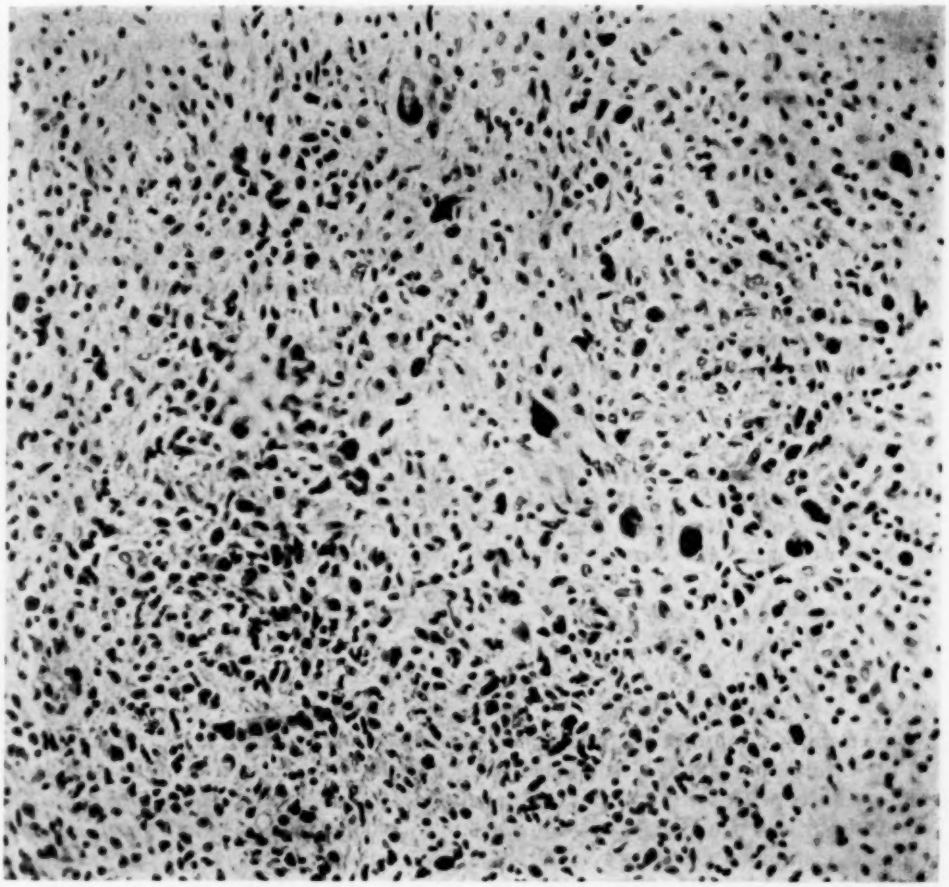

FIG. 2. Higher power photomicrograph of a section through the posterior lobe of the pituitary gland, showing the typical multinucleated Dorothy Reed giant cells of Hodgkin's disease. × 200.

The percentage of hemoglobin and the red and white blood cell counts were normal. Wassermann reaction was negative. The urinalysis was negative except for a low specific gravity, readings varying from 1.004 to 1.008. The urinary output for 24 hour periods varied from 3000 c.c. to 7900 c.c. A urine concentration test revealed poor concentrating power. The blood sugar was 74.1 mg. per 100 c.c. Glucose tolerance tests were normal, the urine on all occasions being negative for sugar.

The temperature was of a relapsing type characterized by elevations reaching 103° F. separated by periods of normal temperature.

Biopsy of a cervical lymph node established the diagnosis of Hodgkin's disease.

For the treatment of Hodgkin's disease, the patient received 12 doses of deep roentgen therapy. Each treatment consisted of 150 r for 6.75 minutes applied alternately to the right groin and left neck. However, the patient showed no favorable response. For the diabetes insipidus, pitressin tannate was given intramuscularly and the polydipsia and polyuria subsided slightly. Before the full effect of this treatment could be determined, the patient developed intestinal obstruction and died.

Autopsy disclosed enlarged lymph nodes in the cervical, axillary and inguinal regions. Some were discrete and others were fused. Section of the nodes revealed a pale gray, homogeneous surface. Examination of the abdominal cavity disclosed an intussusception of the small intestine at the junction of the lower and middle thirds. The intussusception was three inches in length and the exciting cause of the process was a Hodgkin's node. Proximal to this, an area of bowel six inches long was found to be completely necrotic. The remaining small bowel proximal to the necrotic area was markedly dilated and congested. The spleen was enlarged and firm and showed increased fibrosis throughout. The gall-bladder contained a stone about the size of a walnut.

Examination of the cranial cavity disclosed the pituitary gland to be enlarged to about 1.5 cm. in diameter. On section, it was pale gray in color. Both lobes could be differentiated. The sella turcica was intact and no destruction was seen. The surrounding dura mater was not involved.

Histologic examination of a lymph node from the inguinal region disclosed a marked increase in fibrous stroma throughout the section. The lymph follicles were distorted and partly destroyed. Many large mononuclear cells were present with an increase in lymphocytes and eosinophile cells. The spleen disclosed an increase in fibrosis and reticulum cell hyperplasia. The pituitary gland showed infiltration of the anterior and posterior lobes. Both lobes showed a moderate amount of fibrosis. Many large mononuclear cells and some plasma cells were seen. Occasional eosinophile cells were encountered. Many typical multinucleated Dorothy Reed giant cells were also present. The histological picture was characteristic of Hodgkin's disease. Infiltration was more marked in the posterior lobe. A moderate number of neuroglial cells remained in the posterior lobe. The anterior lobe showed one small area of necrosis and many unaltered areas of chromophile and chromophobe epithelial cells.

Discussion

Searching the literature, we encountered only four cases of lymphogranuloma in the pituitary gland. Of these, one did not show symptoms of diabetes insipidus. Three cases in which the diabetes insipidus syndrome developed also showed various neurological symptoms due to involvement of nerve tissue by the lymphogranuloma.

Falta and Spitzenberger (1937) in Germany, reported the case of a woman, aged 42, who was admitted with painful infra- and supraclavicular glands and difficulty in swallowing. Roentgenograms showed mediastinal enlargement. A tentative diagnosis of lymphogranuloma was made. The patient received a course of roentgen therapy and improved. Later, pain developed in the shoulders and arms along with a facial neuralgia, an enlargement of the axillary and inguinal glands, and herpes zoster. Still later, polydipsia and polyuria occurred. Pneumonia developed and death ensued. Autopsy revealed involvement of the mediastinal and mesenteric lymph nodes, the kidneys, the fourth and fifth lumbar vertebrae, the nasopharynx and the pituitary gland with typical lymphogranulomatous tissue.

Desbuquois (1935) in France reported a case of a man, aged 32, who was admitted with cervical adenitis, loss of weight, asthenia and intermittent fever. Roentgenograms showed enlargement of mediastinal lymph nodes. The enlarged nodes were painful, hard, indurated, coalescent and adherent to the deeper structures. Biopsy revealed a lymphogranuloma. Roentgen therapy was instituted and the adenopathy regressed. Polydipsia and polyuria occurred along with symptoms of a cerebral encephalopathy. Roentgen irradiation of the cranium resulted in disappearance of the headaches and a decrease in polyuria. Finally, symptoms of diabetes mellitus, glycosuria and hyperglycemia, occurred. A short time later the patient died. This case presents diabetes mellitus and diabetes insipidus in the same patient, the latter due to the lymphogranuloma.

Flose (1941) in Brazil reported the third case in medical literature. This was an adult with progressive swelling of the right inguinal lymph nodes and three years later, swelling of the left inguinal nodes. Later, there occurred a generalized lymph node hyperplasia and splenic enlargement. Following this, motor and sensory disturbances became apparent, and the lesions were localized to the second, third, seventh, ninth, tenth and twelfth cranial nerves on the left. Roentgenograms showed involvement of the lesser and greater wings of the sphenoid bone. Biopsy of the lymph node revealed a malignant lymphogranuloma. The patient received roentgen therapy and improved temporarily. The motor disturbances disappeared as did the splenic enlargement. Later, the disease became aggravated by a typical diabetes insipidus syndrome due to the localization of the lymphogranuloma in the hypophysis.

Törne (1941) in Germany found a lymphogranuloma of the pituitary gland as an incidental finding in a systematic study of many pituitary glands. Clinical symptoms were missing. The man, aged 73, was admitted for cervical lymph node enlargement and given the diagnosis of generalized lymphogranulomatosis. The patient died of pneumonia and at autopsy was found to have lymphogranulomatosis of the cervical, mental, axillary, mediastinal, mesenteric, preaortic and paragastric lymph nodes. Typical foci were also seen in the spleen, liver, left kidney, pericardium, dura mater, and the pituitary gland. Histology of the lesions disclosed many multinucleated giant cells, many eosinophile leukocytes and fibrous tissue in greater abundance than cellular tissue.

The case reported in this paper shows the similarity in symptoms resulting from a lymphogranuloma involving the pituitary gland. The whole pituitary gland was infiltrated. The posterior lobe was almost completely destroyed whereas the anterior lobe was only moderately involved. This condition is necessary in order for diabetes insipidus to result; that is, the posterior lobe must be destroyed while the anterior lobe must be intact or at least sufficiently functioning. The explanation for this is based on a hormonal control. It has been established that the anterior lobe contains a diuretic hormone and the posterior lobe an anti-diuretic hormone which normally balance one another.

In this case, the neural or posterior lobe involvement caused a diminution or total absence of the anti-diuretic hormone. On the other hand, the pars anterior was involved to a lesser degree and still functioned sufficiently to allow the diuretic factor to act unchecked. Thus we see the reason for the polyuria. Total extirpation of the pituitary gland does not result in diabetes insipidus

because the diuretic factor of the pars anterior is removed along with the anti-diuretic principle of the neural division.

Diabetes insipidus may also result when the lesion is situated anywhere along the hypothalamico-hypophyseal tract. This tract is composed of nerve fibers which run from the hypothalamus to the pars nervosa or posterior lobe. The nerve fibers arise chiefly in the supraoptic nucleus of the hypothalamus and course through the median eminence and infundibulum stem into the pars nervosa and is known more specifically as the supraoptico-hypophyseal tract. A lesion in this tract will cause degeneration of the tract, atrophy of the supraoptic nucleus and atrophy of the neural lobe of the hypophysis.

The present concept of the physiology of diabetes insipidus is well presented in the papers of Fisher, Ingram and Ranson.[3] They support the view that diabetes insipidus is essentially a hormonal disturbance, although the secretion of the anti-diuretic hormone is under the nervous control of the hypothalamus.

The supraoptico-hypophyseal system regulates the secretion of the anti-diuretic hormone by the neural division of the hypophysis. An interruption of this system by a section or lesion may occur at three sites. It may occur in the hypothalamus and cause the neural division (pars nervosa, median eminence, and infundibulum stem) to become atrophic and functionally inactive, thus leading to a deficiency of the anti-diuretic hormone. Likewise, it may occur in the infundibulum stem high enough to cut all of it and the median eminence away from the hypothalamus and bring about a similar atrophy and deficiency. Finally, extirpation or invasion with destruction of the neural division in all its parts leads to the same hormonal deficiency by virtue of the fact that it removes the site of formation of the anti-diuretic principle. This leads to polyuria followed by a secondary and compensatory polydipsia. The polyuria represents the result of diuretic processes in the body unchecked by the anti-diuretic mechanism. These diuretic processes are normally under the control of the pars anterior of the hypophysis. Normally, there is a balance between the diuretic action of the anterior lobe and the anti-diuretic effect of the posterior lobe.

Thus, diabetes insipidus is essentially an hypophyseal deficiency syndrome caused by a diminution or total absence of the anti-diuretic hormone of the neural lobe of the hypophysis. This occurs when the latter is extirpated, destroyed or becomes atrophic secondary to interruption of the supraoptico-hypophyseal tracts, either by a section or a lesion.

Summary

A case of Hodgkin's disease involving the pituitary gland with resulting diabetes insipidus, proved by autopsy, is reported. This is the fourth case in medical literature.

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MAGNESIUM SULFATE IN PAROXYSMAL TACHYCARDIA *

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It has long been known that the magnesium ions act as a depressant to cardiac musculature. Smith, Winkler, and Hoff [1] reported bradycardia, conduction disturbances and eventually cardiac arrest with high concentration resulting from parenteral administration. However, it was not until Boyd and Scherf [2] reported their series of cases that the therapeutic effect and beneficial results of magnesium salts in paroxysmal tachycardia were generally recognized. The effect of intravenous injections of magnesium sulfate in 10 cases of paroxysmal tachycardia and one case of flutter was studied. They found that the injection of a 10 per cent solution was beneficial in three out of eight attacks, whereas a 20 per cent solution was beneficial in eight out of eight attacks. Consequently, the use of a 20 per cent solution was advocated. Disturbances of conduction and ventricular extrasystoles appeared for a short time after the injection. These investigators used 10 to 20 cubic centimeters of the solution for each injection. They recommended that the initial treatment of any attack of paroxysmal tachycardia consist of a trial of the various vagal reflexes. Medicinal therapy is justified only when these reflexes prove useless. Because intravenous quinidine or the use of mecholyl in not always innocuous, they believe that the intravenous use of magnesium sulfate merits a definite place among these drugs in the medicinal management of these disorders. No untoward effects were encountered in their series. Because of the paucity of cases we would like to present another case treated successfully with magnesium sulfate. Also, the dosage of magnesium sulfate used was relatively large according to Boyd and Scherf's recommendations.

Case Report

A. V., 57, white, Italian male, was admitted to the Rhode Island Hospital May 3, 1945. A few hours before admission he was found lying in bed unable to move his right arm or leg. Previous history was negative.

Physical examination showed a well nourished and well developed male who appeared very drowsy. He answered questions with a marked slurring of speech. Blood pressure was 180 mm. Hg systolic and 110 mm. diastolic. There was marked right sided facial weakness and loss of motor power of the right arm and leg. Reflexes were hyperactive on the right side with a positive Babinski and Chaddock on that side. The spinal fluid showed an increase in pressure and uniformly bloody fluid

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in three tubes. The pulse on admission was 88 and his respirations were 22. The diagnosis of subarachnoid hemorrhage and right hemiplegia was made at this time.

Course in hospital: On the third hospital day the patient's pulse suddenly rose to above 200. The apical sounds were very rapid and regular. Radial pulse was felt with difficulty. Carotid sinus pressure and ocular pressure did not alter the pulse rate.

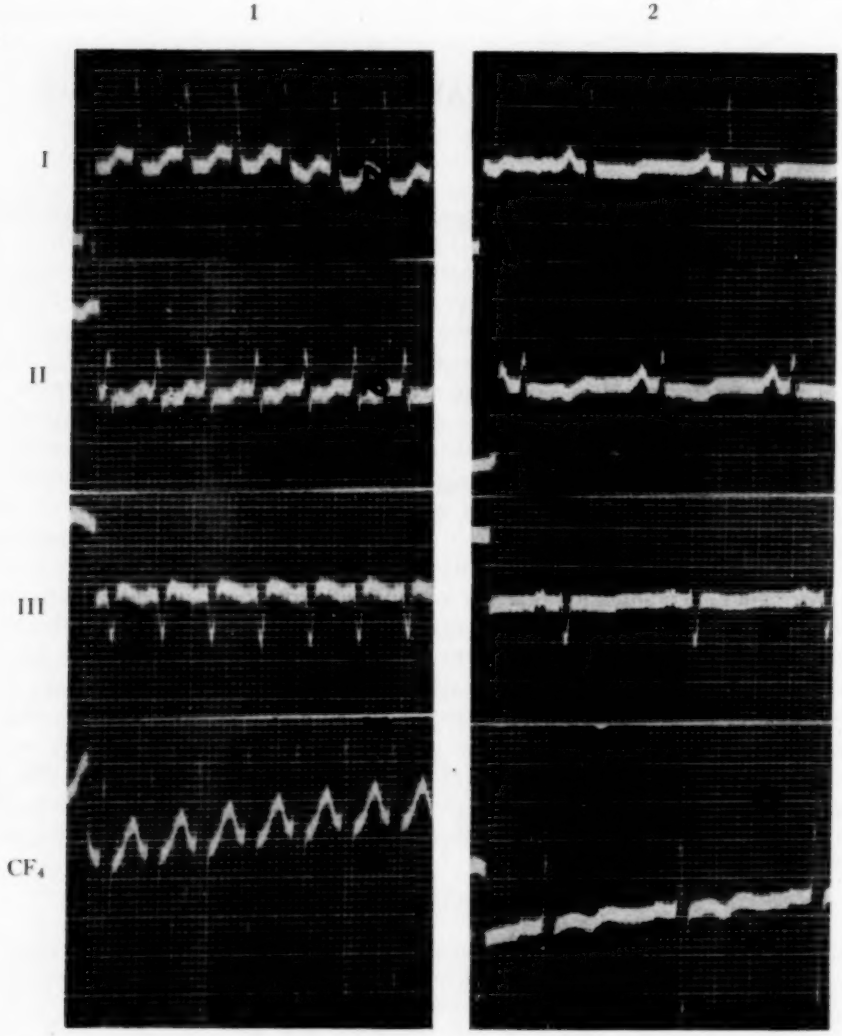

FIG. 1. 1. Before administration of magnesium sulfate. 2. After administration of magnesium sulfate.

An electrocardiogram taken at this time showed a paroxysmal auricular tachycardia with a rate of 240 per minute. Quinidine sulfate, three grains, was started intramuscularly every two hours. He received a total of 18 grains in 12 hours with no effect. Lanatocide-C (Cedilanid), 0.8 mg., was given intravenously and the patient continued on 0.1 gm. of digitalis leaf every four hours. This rapid digitalization also

had no effect. Because of the patient's poor condition it was thought advisable to try to stop the arrhythmia if possible.

Mecholyl was then tried. Twenty-five mg. were given subcutaneously with no effect. Four hours later 10 c.c. of 25 per cent magnesium sulfate were given intravenously with no effect. The patient's temperature had risen to 104° F. by rectum. Six hours later he was given 22 c.c. of 25 per cent magnesium sulfate intravenously. While the needle was still in his vein, his apical beat suddenly slowed to 88 per minute. An electrocardiogram obtained at this time showed regular sinus rhythm with a rate of 76 per minute. The paroxysm had lasted 28 hours. The patient gradually improved and he was continued on digitalis, 0.1 gm. daily.

Summary

1. The effect of intravenous magnesium sulfate on a case of paroxysmal tachycardia is presented.

2. The patient received 10 c.c. of 25 per cent solution with no effect. Six hours later he received 22 c.c. of a 25 per cent solution with immediate cessation of the tachycardia.

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EDITORIAL

FOLIC ACID

ANEMIA developing as a result of a diet deficient in vitamins has been described in a number of species of animals. One of the earliest observations was that of Wills and Bilimoria [1] (1932). Monkeys fed a deficient diet similar to that customarily consumed by the poorer classes in India developed a macrocytic anemia, accompanied by leukopenia, granulocytopenia, and a megaloblastic hyperplasia of the bone marrow, which could be relieved by feeding marmite (yeast extract). This anemia closely resembled that seen in human cases of nutritional macrocytic anemia. This work has been confirmed and extended by subsequent observers, notably by Day and associates.[2] Monkeys on a deficient diet developed a progressive fatal disease characterized by anemia, leukopenia, ulceration of the gums and often diarrhea. This could be prevented by feeding adequate amounts of brewers' yeast or liver extract. To the active substance they applied the term "vitamin M."[3] They together with others later showed that this effect was not produced by any of the recognized members of the vitamin B complex, including thiamin, riboflavin, niacin, calcium pantothenate, pyridoxin hydrochloride, sodium para-amino-benzoate, choline, or inositol.

In 1939 Hogan and Parrott [4] showed that chicks on a special diet adequate in all the essential factors then recognized failed to grow, and developed a macrocytic hyperchromic anemia. This could be prevented or relieved by a water-soluble liver extract. They designated the active substance as vitamin B_c. Similar anemias have been produced in rats and in pigs.

The study of the substance which prevents the development of anemia in these animals has been facilitated and promoted by observations on the growth requirements of certain bacteria. In 1940 Snell and Peterson [5] reported that on a basal medium consisting of hydrolyzed casein, tryptophane and several of the then known members of the vitamin B_2 complex, no growth of *Lactobacillus casei* would occur unless extracts of certain plant or animal tissues were added to the medium. Yeast and liver contained this growth factor (*L. casei* factor) in relative abundance. By adsorption on norite and subsequent elution they were able to remove the active ma-

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[2] DAY, P. L., LANGSTON, W. C., and SHUKERS, C. F.: Leukopenia and anemia in the monkey resulting from vitamin deficiency, Jr. Nutr., 1935, ix, 637.

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terial from these extracts and obtain it in a state of relative purity and high concentration.

In 1941 Mitchell, Snell and Williams [6] obtained from spinach a similar factor which stimulated the growth of *Streptococcus lactis R* (*S. lactis* factor), for which they suggested the name "folic acid" because of the source of the material. This also stimulated the growth of *L. casei* with about the same degree of potency. They devised a method of microbiological assay of these factors which depends in principle upon the determination by titration of the minimal amount of material which stimulates growth of these organisms in the basal medium.

The relationship of the *L. casei* factor to the *S. lactis* factor, and the part they play in the nutrition of animals have been the subject of many investigations which are far too numerous to review here. The subject is complicated, and the identity or exact relationship of the factors obtained by different investigators has not yet been definitely determined. For details the reader is referred to the recent excellent summary of Berry and Spies.[7]

Although the "folic acid" of Snell et al. promoted the growth of these two organisms to about the same degree, other materials were found which stimulated the growth of *S. lactis* but had little or no effect on *L. casei*. If, however, *S. lactis* is allowed to grow in a medium containing such material the supernatant fluid from the culture may be potent in stimulating growth of *L. casei*. With certain other materials the reverse relationship has been observed. An alteration of the factor produced by the growth of one species may be necessary to make it available for the other.

Other materials which have little or no growth-promoting activity for these bacteria (but which may be utilizable by the chick) may become potent if first subjected to the action of an enzyme isolated from certain organs, such as the liver, kidney, pancreas or spleen of the rat or other species of animals. This has led to the hypothesis that the potentially active growth factor occurs in certain extracts in inactive form as a conjugate with other (non-protein) materials. Different organisms apparently vary in their capacity to utilize such material, depending conceivably on their capacity to produce an enzyme which will split the compound and liberate the "active" fraction.

The quantity of active material required to promote growth is very minute, as little as 0.00012 γ of Mitchell's "folic acid" per ml. of medium sufficing to produce half maximal growth of *L. casei*.[6]

The chemical structure of at least one of these growth factors has been determined. Angier et al.[8] have synthesized a compound which appears to be identical in its physiological action (in chicks) and in its important

[6] Mitchell, H. K., Snell, E. E., and Williams, R. J.: The concentration of "folic acid," Jr. Am. Chem. Soc., 1941, lxiii, 2284.

[7] Berry, L. J., and Spies, T. D.: The present status of folic acid, Blood, 1946, i, 271.

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physical and chemical properties with the crystalline *L. casei* factor (folic acid) isolated from liver.

The immediate practical importance of these bacterial growth factors arises from the fact that they are also essential for normal nutrition in animals. It has been shown by numerous investigators that folic acid concentrates will maintain normal growth and prevent or relieve (in large measure, at least) the granulocytopenia, macrocytic anemia and thrombocytopenia that develop in monkeys [9, 10] and chicks [11] kept on the type of deficient diet already described. Folic acid appears to be identical in its physiological action with vitamin M in monkeys and with vitamin B_c in chicks.

In the case of man, early observations, particularly of Wills and other British investigators, showed that certain nutritional macrocytic anemias, including "pernicious anemia" of pregnancy, responded well to marmite and to crude liver preparations (which contain folic acid). In some cases the response was much better to these than to highly purified liver extracts containing Castle's erythrocyte maturing factor.

The effectiveness of *L. casei* factor in curing nutritional macrocytic anemia in monkeys led naturally to a trial in similar anemias in man. Passing by several earlier and less conclusive reports, Vilter, Spies and Koch [12] in 1945 reported the treatment of 14 cases of macrocytic anemia with *L. casei* factor, using the synthetic folic acid. These included six cases of nutritional anemia, five cases of pernicious anemia, and three cases of undetermined nature. The drug was administered both orally and parenterally, usually in an oral dose of 50 mg. twice a day, or parenterally, 20 mg. a day. In all but one case (classed as nutritional anemia) highly satisfactory results were obtained. A reticulocytosis ranging from 6 to 21 per cent appeared, reaching the peak on the fourth to the tenth day. This was accompanied and followed by a progressive rise in red blood cells and hemoglobin, which reached normal in cases in which treatment was continued. In most of those cases with a leukopenia, the leukocytes also rose to normal figures. There was corresponding improvement in clinical symptoms, usually evident subjectively on the third to the fifth day. The patients felt better and stronger, there was a return of appetite and a gain in weight. In some cases there was a cessation of diarrhea when present, and relief from burning of the tongue and oral mucous membranes. Spies [13] has subsequently summarized the results obtained in 27 cases of macrocytic anemia (including the 14 previously mentioned), which were equally favorable.

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[13] Spies, T. D.: Effect of folic acid on persons with macrocytic anemia in relapse, Jr. Am. Med. Assoc., 1946, cxxx, 474.

and regarded as comparable with those obtained with liver extract. Available data are insufficient to determine whether folic acid is equally effective, and there is now no reason to believe that it will prove superior to liver extract. In two patients with pernicious anemia who had become sensitized to liver extract, folic acid was substituted "safely and satisfactorily."

Folic acid was without effect in three cases of aplastic anemia, four cases of iron deficiency anemia and three cases of anemia due to leukemia.

In these cases, the response to oral administration was regarded as somewhat better than to parenteral injections, but the oral dose was five times as large. Spies states that marked responses have been obtained in some cases with as little as 10 mg. per day by mouth and 5 to 10 mg. parenterally. The minimal effective dose and the optimal dose have not been determined, but 400 mg. per day has been given orally without bad effects. It does not affect the blood of normal individuals.

Confirmatory reports by other observers have recently appeared. Moore et al.[14] reported successful treatment of four cases, including two cases of pernicious anemia. Doan et al.[15] report obtaining satisfactory clinical results with synthetic *L. casei* factor in selected cases, and report one case of pernicious anemia which gave a maximal response to 2 mg. per day intravenously over a period of 20 days. (Spies, however, has observed cases in whom 3 to 4 mg. a day did not cause a satisfactory response.) In three cases hypersensitive to liver extract, folic acid was substituted with satisfactory results.

Amill and Wright[16] also have reported the successful treatment of six unselected cases of pernicious anemia with synthetic *L. casei* factor.

Highly satisfactory results have also been obtained in treatment of sprue. Darby et al.[17] reported the successful treatment of three cases with synthetic *L. casei* factor. Spies and associates[18] reported the successful treatment of nine cases of tropical sprue in Cuba. A more complete report of this work was presented at the meeting of the American College of Physicians (May, 1946) and will be published in an early number of the Annals of Internal Medicine.

The hematopoietic response in these cases was quite like that in the other types of macrocytic anemia. There was a reticulocytosis ranging from 12.5 to 32 per cent, which was a maximal response according to the

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standard of Minot and Castle for liver extract in pernicious anemia. There was a progressive rise in hemoglobin and in red blood cells, ranging from 0.46 to 1.2 million in 14 days. In three cases examined the marrow reverted to a normoblastic type of hyperplasia. There was a corresponding improvement in subjective symptoms, with increased appetite, gain in weight and strength and increase in vigor and alertness. The burning and objective evidences of glossitis subsided. In most cases the diarrhea largely or entirely subsided, and the feces tended to return to normal in bulk and gross appearance. Usually, however, the stools did not become completely and permanently normal. The period of observation, however, has been relatively short, and the (experimental) diet not optimal and probably deficient in some other respects.

Three patients who were given 10 mg. a day responded about as well as those who received 100 mg.

The mechanism of the action of folic acid and its relation to other known hematopoietic factors have not been demonstrated. Since it is active on parenteral injection, folic acid can not be the intrinsic factor of Castle. For the same reason and because it does not depend upon the action of gastric juice for its activity it is probably not identical with extrinsic factor, although it is still possible folic acid may be related in some way to the latter. It is probably not the active material (E. M. F.) in liver, since the required dose of folic acid is many times larger than the amount contained in an effective dose of potent liver extract. To go farther than this is to indulge in what is largely speculation. Spies,[7] however, has advanced the interesting suggestion that folic acid may be ingested and possibly stored in the tissues in the form of an inactive conjugate. In pernicious anemia there may be a lack of enzymes which can split off the folic acid. Potent liver extract may act by liberating the active fraction in utilizable form. It seems likely that folic acid in some way functions as part of an essential enzyme system, and that its rôle is not limited to its hematopoietic functions.

The part that folic acid will take in practical therapeutics is still uncertain, particularly the extent to which it may supplant the use of liver extracts. It is not yet certain that folic acid is fully equal to liver extract in maintaining remissions, and particularly in preventing the development of neurological degenerations in pernicious anemia. It seems improbable that it will be any more effective. Apparently folic acid is a satisfactory substitute, at least for a short period, in patients who are hypersensitive to liver extracts. If it proves to be as effective as liver extract, it will have an important advantage from the pharmaceutical standpoint in eliminating the difficulty—which is getting increasingly urgent and acute—of finding enough untreated cases of pernicious anemia on whom to test the potency of commercial liver extracts.

REVIEWS

The Physiological Basis of Medical Practice. By CHARLES HERBERT BEST, C.B.E., M.A., D.Sc. and NORMAN BURKE TAYLOR, V.D., M.D., F.R.S. Fourth Edition. 1169 pages; 26.5 × 17 cm. 1945. Williams & Wilkins Co., Baltimore. Price, $10.00.

The continued success of "The Physiological Basis of Medical Practice" is shown in the demand which has necessitated thirteen printings and four editions in eleven years. The format of this edition has been changed. Double columns and larger pages make it easier both to read and to handle. The moderated reduction in the size of many of the diagrams and illustrations, together with the deletion of outmoded material has made room for much new material without a marked increase in the size of the volume.

The chapter on intracellular oxidations by Dr. Wyne has been markedly improved by rewriting. Much more material is included than in the previous editions and it is presented in a more systematic fashion. A number of type reactions are shown which demonstrate oxidative systems and a new diagram (from Potter 1944) shows the inter-relationships between the phosphorylating, glycolytic and respiratory systems.

The references are grouped by chapters at the end of the book. They are divided into two sections: specific references to original articles and monographs and reviews. The material is carefully cross indexed. The few errors found in no way detract from the value of the volume.

M. A. A.

About Ourselves. By JAMES G. NEEDHAM, Ph.D. 276 pages; 26 × 18 cm. 1941. Jaques Cattell Press, Lancaster, Pa. Price, $3.00.

This book might be considered an introduction to the study of sociology, written from the viewpoint of a zoölogist. The author presents, in a simple, non-technical form, the contributions of zoölogy to the knowledge of the human species, together with his thinking as to the relation of this knowledge to the organization of society. The book is divided into two parts: Part I, "Man in His Biological Aspects", is an excellent summary of man's evolution and place in the animal world, the similarities and difference between us and other animals, the development of human behavior, and the nature of instincts. Par II, "Society in Its Biological Aspects," discusses the distinction between man's social and biological inheritance, traces the development of socially determined behavior (always relating this to the instinctive needs out of which it arose) and ends with some chapters on war, government and religion in their biological aspects.

Part I and sections of Part II are written with a simplicity and clarity which obviously arise from the author's thorough familiarity with his subject. Particularly valuable is the exposition of instinctive behavior which includes a thoughtful discussion of the characteristics of instincts, profusely illustrated with recollections and ancedotes of the barnyard, zoo, jungle, nursery, and battlefield. One feels that Dr. Needham's thoughts on instinctive behavior are written by one who has watched it with joy and fascination for a long time. There is something about it that is missing from the rather theoretical treatment often given this subject by the psychologist, psychiatrist or sociologist. Part II deals with problems of war and peace in an interesting way. The author develops the picture of man as a fighting animal,

states that ". . . instinct in man as in animals yields only to force", and that there must be a high command to preserve international order. He uses the organization of body cells to support his belief that mutual dependence, mutual coöperation, and an organ of control are essential to peace, which he defines as organic health. The latter part of this book contains a good deal of homespun philosophy which is thoughtful but, to this reader, somewhat lacking in recognition of the contributions which have been made by the social sciences to the understanding of problems which are discussed. For example, Dr. Needham says, "Men and nations fight, as do animals, when well armed, well fed, well conditioned generally, and when there is nothing much worthwhile to fight about."

Modern social thinkers would be inclined to believe that we could always find that there was something to fight about, were we capable of understanding it, and much work has been done in an effort to study the relationship between aggression and the frustrations of our culture. Dr. Needham hints at this, but does not discuss it with the same authority and clarity which he demonstrates in the first part of the book.

"About Ourselves" should serve as a useful "refresher" for those who have become immersed in advanced work in any of the biological or sociological fields. It should also be valuable as orientation reading for the layman or for college students.

H. W. N.

The Vitamins in Medicine. By FRANKLIN BICKNELL, D.M., M.R.C.F., and FREDERICK PRESCOTT, M.Sc., Ph.D., A.R.I.C., M.R.C.S., Clinical Research Director, The Wellcome Foundation, London. Second Edition. 23.5 × 16 cm. 1946. Grune and Stratton, New York City. Price, $12.00.

The second edition of "The Vitamins in Medicine" follows the first within four years. The marked advances in knowledge in this field have been particularly noticeable in the studies on the B complex. Twenty-two members have now been identified either as chemical entities or by their biological effect on various experimental animals. These advances have necessitated a complete revision of the section on these vitamins. It has been pointed out that a number of the vitamins of the B complex which have been characterized only by their biological activity may prove to be identical with some of the known factors of the B complex or mixtures of known amino acids, so that ultimately the number of factors may be decreased. The author presents a useful chart showing the chronological resolution of the B complex into its various fractions.

Two new chapters have been added on the unsaturated fatty acids and the minor fat soluble vitamins. It has been pointed out that the designation of the so-called essential fatty acids (linoleic, linolenic, and arachidonic) is somewhat ambiguous since any one of these acids can replace the other two in the diet. The only condition in which these acids appear to be important is in eczema.

The vitamin tables have been revised in the light of recent standards. Units are given where possible in micrograms or milligrams as well as in international units. When other units are in use the coversion factors are also presented if possible.

The authors have covered the clinical literature very thoroughly and have included over 4,500 references. The volume is exceptionally well indexed. It is one of the most complete works in this field that has been published and is an exceptional reference volume.

M. A. A.

Mental Health in College. By CLEMENTS C. FRY, M.D., with the collaboration of EDNA G. ROSTOW. 395 pages; 23.5 × 15.5 cm. The Commonwealth Fund, N.Y.C. 1942. Price, $2.00.

After ten years of experience, from 1926 to 1942, the authors have described and evaluated the psychiatric service offered to students of Yale University by the Division of College Psychiatry and Mental Hygiene, of the Department of University Health. In common with all other types of psychiatric service, this mental health program has encountered in educators, parents, patients and others, attitudes of indifference, popular prejudice, specific objections and the usual conviction that all that is needed to solve mental health problems is a generous application of "good common sense." Of the 1257 Yale students receiving psychiatric service, 787 were undergraduates, with 45 per cent coming from the freshman class, and the remaining 470 were enrolled in the Graduate School and the Schools of Fine Arts, Divinity, Law, Medicine, Nursing, Music and Forestry. As a group, these patients constituted a cross-section of the university population, including "Phi Beta Kappa and low-stand students; rich and poor; socially prominent and the reverse; the varsity athletes and the unathletic; senior society and fraternity members, and those who do not belong to any special groups."

In 1141 of the cases studied and treated, "these students looked upon themselves and were regarded by others as 'normal people,' but they reacted at times in much the same way as so-called 'abnormal' patients." Responding to stresses in separation from homes and families and adjustment to college demands during "a period usually coinciding with the climax of adolescent changes in their physical, impulsive, emotional and intellectual lives," these students developed behavior disorders, gastrointestinal upsets, fatigue, insomnia and periods of anxiety and depression. Psychoses and other serious psychopathies were encountered in 116 students, or 8 per cent of the case load. Even among these, a considerable number recovered after a time and completed their college course. Fifty-three per cent of the students were seen from one to three times by the psychiatrist, while the remaining 47 per cent were interviewed more or less regularly for a month, several months or years.

In the area of family relationships, emotional conflicts may arise in attempts to grow up and achieve independence in the face of pressures and demands by dominating parents, parents who desire to absorb, possess and supervise their sons, or who have abnormal attachments to them. Friction between parents in the home, or separated parents, rejection by parents and other vicissitudes or crises in family life may markedly affect students' personalities and college adjustments. The students are also emotionally engaged with problems of sexual growth, behavior and attitudes. Difficulties in this area were related to petting, masturbation, heterosexual experimentation, promiscuity, adjustments in courtship or marriage, fears of homosexuality and homosexual activities. Because "the community limits the dissemination of proper information, tolerates the spread of false notions and inculcates a fear of sex," the student's view of sex "is compounded of misinformation and taboo." The consequent "feelings of inferiority, of alarm, of guilt, of shame, of depression, and of anxiety—may be intensified by ignorance, often with serious consequences."

For many entering students, emotional problems develop in relation to the demand for scholastic success. Lack of ability or ambition, inadequate scholastic training and preparation for independent work, the demands and pressures exerted by families, financial handicaps, social maladjustment or over-valuation of social success and other personality problems play an important rôle in academic failures. Upper-classmen and graduates may also face failures for similar or related reasons. In relation to problems of social adjustment in the college society, the authors state

that "recognition, acceptance, and approval by the group are, of course, the social objective of all students, for such acceptance represents a long step, in any society, toward security for most individuals," and "social success cannot be under-estimated in any consideration of the college community." Boys who are handicapped by self-consciousness, shyness and social awkwardness, by previous experience of protected absorption in family life, by rejection by the family, by differences in social background and lack of social experience, financial pressure and other personality handicaps, often develop emotional upsets and mental health problems.

Although some cases are presented in considerable detail, many seem sketchy and the value of this book lies more in the general discussion of the varied mental health problems of college students. Separate presentation of the problems of freshmen, upperclassmen and graduate students leads to considerable overlapping and repetition. The book, however, will be of great value to all those engaged in the education and guidance of youth in high schools, colleges and universities, and to physicians, parents and others who are interested in the treatment and prevention of problems of adjustment among these age groups.

C. B.

Alteracões Hepáticas na Tireotoxicose. By P. A. DA COSTA COUTO. 278 pages; 23.5 × 16 cm. 1944. Borsoi, Rio de Janeiro.

This monograph is based on a three year study of hepatic changes noted in hyperthyroidism. The literature is thoroughly reviewed and the bibliography complete. The author is not impressed by jaundice, reported by others as a common feature in thyrohepatic disturbances. The Quick hippuric acid synthesis test and the Bauer galactose tolerance test uniformly indicated liver cell function disturbance. Thus the mechanisms disturbed were the "antitoxic" and glycogen storage.

A correlation between the thyroid and liver is generally recognized, but no signal evidence of this relationship outside of jaundice which occurs uncommonly is identifiable in the clinical picture of hyperthyroidism. Widespread hepatic lesions occur in the severe types of thyroid dysfunction. There is a direct correlation between the severity of the symptoms and the underlying endocrine and metabolic disturbances.

The necropsy findings in two instances of hyperthyroidism are described. These conform to other published accounts. Congestive changes in the liver sinusoids and cellular changes approaching necrosis are well illustrated. Similar lesions occurring in guinea pigs poisoned with thyroid substance or thyroxin are also reproduced excellently.

Great significance is attached to the hepatic status in fatal Graves' disease or thyroid storm. Analogy is made to the hepatorenal syndrome.

The recognition of the thyrohepatic correlation is necessary, in the author's opinion, for therapeutic orientation, both in the pre- and post-operative periods of hyperthyroidism.

da Costa Couto recommends a regimen which restores the functional equilibrium of the liver. Carbohydrate, liver extract and vitamins A, B, and C are among these measures.

No new data appear in this extensive monograph. The material presented is well handled. The unqualified stand on the importance of hepatic dysfunction in thyroid storm is not supported by proved data. The emphasis on joint treatment of thyroid and hepatic dysfunction in all phases of hyperthyroidism is the commendable theme of this work.

S. S. L.

BOOKS RECEIVED

Books received during July are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

The Venereal Diseases. By JAMES MARSHALL, M.B., B.S., M.R.C.S. 348 pages; 22 × 14.5 cm. 1946. The Macmillan Company, New York. Price, $4.50.

Anesthesia in General Practice. By S. C. CULLEN, M.D. 259 pages; 21 × 14.5 cm. 1946. Year Book Publishers, Inc., Chicago. Price, $3.50.

Peptic Ulcer; Its Diagnosis and Treatment. By I. W. HELD, M.D., and A. ALLEN GOLDBLOOM, M.D. 382 pages, 25 × 16.5 cm. 1946. Charles C. Thomas, Springfield, Ill. Price, $6.50.

The Endeavor of Jean Fernel. By Sir CHARLES SHERRINGTON, O.M. 223 pages; 22.5 × 14.5 cm. 1946. Cambridge University Press, The MacMillan Company, New York. Price, $3.50.

The Child from Five to Ten. By ARNOLD GESELL, M.D., Director Yale Clinic of Child Development, and FRANCIS L. ILG, M.D., Asst. 475 pages; 25.5 × 18.5 cm. 1946. Harper & Brothers, New York. Price, $4.00.

Currents in Biochemical Research. Edited by DAVID E. GREEN. 486 pages; 24 × 16.5 cm. 1946. Interscience Publishers, Inc., New York. Price, $5.00.

Mother and Baby Care in Pictures. Third Edition. By LOUISE ZABRISKIE. 203 pages; 23.5 × 16 cm. 1946. J. B. Lippincott Company, Philadelphia. Price, $2.00.

The American Hospital. By E. H. L. CORWIN, Ph.D. 226 pages; 21.5 × 14 cm. 1946. The Commonwealth Fund; New York. Price $1.50.

Urologic Roentgenology. Second Edition Revised. By MILEY B. WESSON, M.D. 259 pages; 24 × 15 cm. 1946. Lea & Febiger, Philadelphia. Price, $5.50.

Narco-Analysis. By J. STEPHEN HORSLEY. 134 pages; 19 × 13 cm. 1946. Oxford University Press, New York. Price, $2.50.

Lippincott's Quick Reference Book for Medicine and Surgery. Thirteenth Edition. By GEORGE E. REHBERGER, A.B., M.D. 1461 pages; 26 × 18 cm. 1946. J. B. Lippincott Company, Philadelphia. Price, $15.00.

COLLEGE NEWS NOTES

New Life Members of the College

The College is gratified to announce the following additional Life Members listed in the order of subscription:

Dr. Morris Deitchman, Youngstown, Ohio
Dr. George Foster Herben, Yonkers, N. Y.
Dr. Arthur Ernest Moon, Temple, Tex.
Dr. Gustav L. Kaufmann, Chicago, Ill.

Gifts to the College Library

The following gifts of publications by members are gratefully acknowledged:

Dr. G. S. Backenstoe, (Associate), Emmaus, Pa.—4 reprints
Dr. Arthur Bernstein, F.A.C.P., Newark, N. J.—1 reprint
Dr. Louis F. Bishop, Jr., F.A.C.P., New York, N. Y.—1 reprint
Dr. Robert G. Bloch, F.A.C.P., Chicago, Ill.—7 reprints
Dr. Benjamin Burbank, F.A.C.P., Brooklyn, N. Y.—5 reprints
Dr. Nathan Smith Davis, III, F.A.C.P., Chicago, Ill.—13 reprints
Dr. Herbert R. Edwards, F.A.C.P., New York, N. Y.—13 reprints
Dr. William E. Jahsman, F.A.C.P., Ferndale, Mich.—1 reprint
Dr. Samuel R. Kaufman, F.A.C.P., Wilkes-Barre, Pa.—1 reprint
Dr. William David King, F.A.C.P., Phoenix, Ariz.—1 reprint
Dr. Rudolph A. Kocher, (Associate), Carmel, Calif.—1 reprint
Dr. Emanuel Klosk, (Associate), Newark, N. J.—1 reprint
Dr. Thomas H. McGavack, F.A.C.P., New York, N. Y.—5 reprints
Dr. Samuel Millman, F.A.C.P., Brooklyn, N. Y.—2 reprints
Dr. Edward W. Miskall, F.A.C.P., East Liverpool, Ohio—1 reprint
Dr. William J. O'Connel, Jr., (Associate), East Providence, R. I.—1 reprint
Dr. B. M. Overholt, F.A.C.P., Knoxville, Tenn.—1 reprint
Dr. Aaron E. Parsonnet, F.A.C.P., Newark, N. J.—1 reprint
Dr. Merritt H. Stiles, F.A.C.P., Spokane, Wash.—6 reprints
Dr. Leon N. Sussman, (Associate), New York, N. Y.—1 reprint
Dr. Harry Warshawsky, (Associate), Dayton, Ohio—1 reprint
Dr. Alexander Wiener, F.A.C.P., Brooklyn, N. Y.—13 reprints
Dr. I. Milton Wise, F.A.C.P., Mobile, Ala.—4 reprints
Dr. Andrew C. Woofter, F.A.C.P., Parkersburg, W. Va.—3 reprints
Dr. Paul H. Wosika, (Associate), Chicago, Ill.—5 reprints

The College further acknowledges with deep gratitude the receipt of a complete set of the American Journal of the Medical Sciences from its inception, the gift being made by Dr. Louis F. Bishop, Jr., F.A.C.P., of New York City. This journal was originally collected and owned by Dr. Bishop's father, the late Louis Faugeres Bishop, F.A.C.P., and is added to the College Library as a memorial to him. This rare set of this journal will prove increasingly valuable as the years go by.

The Nineteenth Graduate Fortnight of the New York Academy of Medicine will occur October 7–18, 1947. The subject of the program will be Tumors. The

program will consist in morning panel discussions, afternoon hospital clinics, evening addresses, scientific exhibits and demonstrations. Registration cards will be supplied to Fellows of the Academy without charge, and medical officers engaged in active service will not be required to register. All others may receive registration cards upon payment of a fee of $5.00.

Dr. Charles L. Brown, F.A.C.P., Professor and Head of the Department of Medicine of the Temple University School of Medicine, will assume the duties of Dean of the Hahnemann Medical School and Hospital of Philadelphia, September 1. Dr. Brown received his medical degree at the University of Oklahoma School of Medicine and is a Diplomate of the American Board of Internal Medicine. He has held appointments in the Peter Bent Brigham Hospital and the Children's Hospital, Boston, and in the Harvard Medical School and the University of Michigan School of Medicine. Dr. Brown is a Fellow of the American Association for the Advancement of Science and of the American Medical Association. Among the societies of which he is a member are the American Society for Clinical Investigation, the Central Society for Clinical Research, the Physiological Society of Philadelphia, and the American Heart Association.

Dr. George C. Wilson, F.A.C.P., has accepted appointment as Assistant Chief of the Tuberculosis Division Branch No. 1, Veterans Administration, Boston, Mass. Formerly a resident of Norwich, Conn., Dr. Wilson has removed to Waban, Mass.

Announcement has been received of the Seventh Annual Congress on Industrial Health, which will be held September 30–October 3, 1946, at the Copley-Plaza Hotel, Boston, Mass. The sponsor of the Congress is the Council on Industrial Health of the American Medical Association.

Dr. Francis R. Dieuaide, F.A.C.P., who recently became scientific director of the Life Insurance Medical Research Fund, formerly a resident of Boston, Mass., may henceforth be addressed in care of the Fund at 2 E. 103rd St., New York 29, N. Y.

The Sixth Annual Session of the American Diabetes Association was held September 16–18, 1946, in Toronto, Ont., Can. Drs. Joseph H. Barach, F.A.C.P., Pittsburgh, and R. M. Wilder, F.A.C.P., Rochester, Minn., president and incoming president, respectively, of the Association, presided over the sessions.

The program of the first day commemorated the twenty-fifth anniversary of the discovery of insulin. Among the speakers of the day were Drs. David P. Barr, New York, President of the American College of Physicians; Seale Harris, F.A.C.P., Birmingham; E. P. Joslin, F.A.C.P., Boston; and R. M. Wilder.

The second day's program concerned the accomplishments of the past twenty-five years. Papers were presented by Drs. Frank N. Allan, F.A.C.P., Boston; F. B. Peck, F.A.C.P., Indianapolis; I. M. Rabinowitch, F.A.C.P., Montreal; and Priscilla White, F.A.C.P., Boston.

The third day featured reports of recent investigative work and an open forum.

Dr. Ben E. Grant, F.A.C.P., formerly of Los Angeles, Calif., has accepted appointment as Chief Medical Officer of the Veterans Administration Hospital, Vancouver, Wash.

Dr. Samuel J. Prigal, (Associate), New York, was awarded the Merrit H. Cash Prize for 1946 by the Medical Society of the State of New York, for his essay entitled: "Studies with Medicated Aerosols: The Use of the Lungs as a Portal for the Introduction of Therapeutic Agents for Systemic Effects".

The Medical Consultants Division of the Office of the Surgeon General, Colonel Arden Freer, F.A.C.P., Director, has announced the appointment of sixteen civilian physicians as consultants in internal medicine to the Secretary of War. Of these, thirteen are Fellows, and one an Associate of the College. They are: Dr. E. V. Allen, Rochester, Minn.; Dr. Worth B. Daniels, Washington, D. C.; Dr. George B. Denney, Boston, Mass.; Dr. Eugene P. Eppinger, Boston, Mass.; Dr. Joseph M. Hayman, Jr., Cleveland, Ohio; Dr. Walter B. Martin, Norfolk, Va.; Dr. John Minor, Washington, D. C.; Dr. Hugh J. Morgan, Nashville, Tenn.; Dr. William T. Rainey, Fayetteville, N. C.; Dr. George P. Robb, Washington, D. C.; Dr. Monroe J. Romansky, (Associate), Silver Spring, Md.; Dr. Virgil Sydenstricker, Augusta, Ga.; Dr. Henry M. Thomas, Jr., Baltimore, Md.; Dr. Irving S. Wright, New York, N. Y.

Dr. John Minor, F.A.C.P., Washington, D. C., has been awarded the Legion of Merit. The award was made in recognition of Dr. Minor's services while Colonel in the Medical Corps, AUS, as Medical Consultant to the Surgeon of the Third Service Command. The announcement of this award contained the following statement: "He raised the professional standards of the various hospitals of this command to a high degree of efficiency by his leadership and exceptional professional ability".

Dr. Philip K. Arzt, (Associate), Jamestown, has been elected to the position of president-elect of the North Dakota State Medical Association.

Drs. Hugh B. Campbell, F.A.C.P., Norwich, Conn., and Horton C. Hinshaw, F.A.C.P., Rochester, Minn., have been elected Vice Presidents of the National Tuberculosis Association. Dr. Herbert R. Edwards, F.A.C.P., New York, has been elected Secretary of the association.

Dr. James M. MacMillan, (Associate), formerly of Detroit, has moved to Richmond, Va., and will be associated there in the practice of internal medicine, particularly gastro-enterology, with Dr. Charles M. Caravati, F.A.C.P.

Recent appointments as consultants to the Richmond Branch Medical Service of the Veterans Administration included Drs. Dean B. Cole, F.A.C.P., and R. F. Gayle, F.A.C.P., of Richmond, Va., the former as consultant in tuberculosis and the latter as consultant in neuropsychiatry. Dr. Benjamin M. Baker, Jr., F.A.C.P., Baltimore, Md., received appointment as consultant in internal medicine.

Advance information received concerning the program for the 1946 meeting of the Mississippi Valley Medical Society gives the following Fellows of the College as speakers: Drs. Robert E. Britt, G. O. Broun, Ralph A. Kinsella, LeRoy Sante, and W. Barry Wood, Jr., all of St. Louis; M. Herbert Barker, Robert S. Berghoff, and Israel Davidsohn, all of Chicago; and H. Corwin Hinshaw, Rochester, Minn. The meeting will take place at the Hotel Jefferson, St. Louis, September 25–27. Dr. Harold Swanberg is secretary of the society.

Dr. Edward Weiss, F.A.C.P., Philadelphia, addressed the medical section of the American Life Convention at its meeting June 20 at Hot Springs, Va., on the subject, "Psychosomatic Aspects of Chronic Disease".

Dr. George Morris Piersol, Secretary General of the American College of Physicians, has been elected Vice President of the Pennsylvania Academy of Physical Medicine for the year 1946–47.

Schenley Institute Awards Fellowships

The Schenley Research Institute, which is affiliated with Schenley Distillers Corporation and Schenley Laboratories, Inc., has announced an allocation of $110,000 to support a number of three-year postgraduate fellowships to be awarded by the University of Wisconsin. It is the plan of the Institute and of the University that these fellowships shall be for the conduct of basic scientific research in the field of production and mode of action of antibiotics. The stipends will be of the order of $3,600 to $4,000 a year and, in addition, the Institute will provide the University with allowances for the research expenses of the Fellows. The Fellows will work under the supervision of members of the University's Departments of Agriculture, Bacteriology, Biochemistry, Plant Pathology, Veterinary Science and Botany.

Dr. Henry R. Carstens, F.A.C.P., Philadelphia, Director of Medical Service, Veterans Administration, Branch No. 3, has announced that by agreement among the Army, Navy and Veterans Administration, 41 Army and Navy physicians will soon report for duty in Veterans Hospitals in Pennsylvania, New Jersey and Delaware.

Dr. John D. Davis, F.A.C.P., retired from the Army of the United States with the rank of Colonel, and has accepted an appointment as Chief of the Chest Diseases Service, and Chief of the Medical Service, in the Veterans Administration at Birmingham General Hospital, Van Nuys, Calif.

Brigadier General William L. Hart, U.S.A., Retired, F.A.C.P., Washington, D. C., has been appointed Dean of the Southwestern Medical College, Dallas, Tex. Dr. Hart assumed this position on August 1, succeeding Dr. Tinsley R. Harrison, F.A.C.P. Dr. Harrison will continue to serve the College as Professor of Internal Medicine.

Dr. William S. Middleton, F.A.C.P., Madison, Wis., has been made an Honorary Fellow of the Royal Society of Medicine.

The formation of an Antibiotic Study Section has been announced by the National Institute of Health, Bethesda, Md. The following Fellows of the College have been made members of the section: Dr. David P. Barr, New York; Capt. George B. Dowling, Washington, D. C.; Dr. W. Barry Wood, Jr., St. Louis, Mo.

Schering Corporation, Bluefield, New Jersey, has announced that it will send to interested physicians, upon request, a portfolio of illustrations by the noted artist, Rockwell Kent, of patients suffering from specific endocrine deficiencies.

Dr. Clarence E. de la Chapelle, F.A.C.P., New York, has been appointed Associate Dean of the New York University College of Medicine. Dr. de la Chapelle has held the positions of Professor of Clinical Medicine, Assistant Dean, and Director of the Postgraduate Division of the College of Medicine.

The Distinguished Service Medal of the American Medical Association has been awarded to Dr. Anton J. Carlson, F.A.C.P., Chicago, Ill. This tribute to Dr. Carlson, long an active member of the faculty of the University of Chicago, and of the American College of Physicians and the American Medical Association, recognizes Dr. Carlson's outstanding services to medical research and to medicine.

Drs. Jack C. Norris, F.A.C.P., Atlanta, and Ernest F. Wahl, F.A.C.P., Thomasville, have been appointed by Governor Arnall of Georgia to membership on a board to determine medical questions pertaining to workmen's compensation.

Dr. A. C. Ivy, F.A.C.P., Chicago, has been appointed to succeed Dr. Raymond V. Allen, F.A.C.P., as Vice President in charge of the Colleges of Medicine, Dentistry and Pharmacy, and hospitals and institutes of the University of Illinois in Chicago. Dr. Ivy has also been appointed to the position of Distinguished Professor of Physiology in the University's Graduate School. Dr. Ivy has served with distinction the Northwestern University Medical School, in which he has held since 1925 the title of Nathan Smith Davis Professor of Physiology and Pharmacology. During World War II, Dr. Ivy was Director of the Naval Medical Research Institute, Bethesda, Md., and served also as consultant to the War and Navy Departments.

Dr. Robert O. Brown, F.A.C.P., is the recipient of a citation of merit awarded by alumni of the University of Chicago on June 8.

Dr. Alonzo Frederick Brand, F.A.C.P., has been commissioned in the regular corps of the U. S. Public Health Service with the rank of Senior Surgeon and is now the Venereal Disease Control Adviser for the Philippines. Dr. Brand previously held a commission as Lieutenant Colonel and was assigned to the U. S. Public Health Service Reserve.

Dr. Harold J. Kullman, F.A.C.P., recently assumed a full time position as Chief of Medical Service at the Veterans Administration Hospital, Dearborn, Mich.

Captain Ceres Receives Legion of Merit

Captain Frederick Ceres, (MC), USN, F.A.C.P., received the Legion of Merit with the following citation from Admiral Chester W. Nimitz, Commander-in-Chief of the U. S. Pacific Fleet:

Citation:

"For exceptionally meritorious service in a position of great importance and responsibility as Medical Officer in Command of the U. S. Naval Hospital, Aiea Heights, Territory of Hawaii, from 2 August 1943 to 4 July 1944. He personally supervised the extensive expansion his command required for the hospitalization of

the large numbers of wounded from combat areas in the Central Pacific, thereby contributing materially to the rapid rehabilitation of personnel essential to successful prosecution of the war against Japan. During this entire period, he habitually displayed sound judgment, tireless energy, zeal, and initiative, thereby succeeding in developing and maintaining his hospital as the outstanding institution of its kind in this area. Throughout his tour of duty in the Fourteenth Naval District, Captain Ceres has maintained the highest standards of efficiency and morale within his command in keeping with the finest traditions of the naval service."

Appointments Open

A Fellow of the American College of Physicians who is now superintendent of a large State Hospital in Kentucky, has applied to the College to refer to him some competent young man of character and ability who desires work in neuropsychiatry. The hospital is a modern institution, ideally situated and there are several openings. Any interested physicians should communicate with the Executive Secretary of the College, Mr. E. R. Loveland, 4200 Pine Street, Philadelphia 4, Pa., making reference to "AO–3."

Dr. Thomas T. Mackie, F.A.C.P., formerly of New York City, has accepted an appointment as Professor of Preventive Medicine and Chairman of the Division of Medicine at the Bowman Gray School of Medicine, Winston-Salem, N. C. Dr. Mackie recently returned from England. He served during World War II as a Colonel in the Army. He is President of the American Foundation for Tropical Medicine.

Naval Citation to Dr. Dar D. Stofer, F.A.C.P.

Dr. Dar D. Stofer, F.A.C.P., now of Monterey, Calif., received toward the end of his Naval service in April, 1946, the following citation from the Surgeon General of the U. S. Navy. Dr. Stofer was a Captain in the Naval Reserve:

"Your outstanding performance of duty as a medical officer on duty at U. S. Naval Mobile Hospital No. 6 in New Zealand, is considered worthy of special commendation.

"Your superior professional qualifications in internal medicine, and your sustained interest, diligence and coöperation as Chief of the Medical Service made possible a thorough medical study of all neuro-psychiatric cases in the hospital and, by the elimination of organic disease, contributed largely to the successful treatment and return to combat of an unusually high percentage of neuroses and combat fatigue patients.

"I commend you for exceptional ability, resourcefulness and outstanding devotion to duty which reflected credit upon yourself and the Naval Service."

Capt. Julian Love, (MC), USN, F.A.C.P., was stationed at Kwajalein, Marshall Islands, during the atomic bomb tests at Bikini, and witnessed the B bomb experiment from a 7500′ altitude on a plane, some seven miles slant range from the target.

The Twenty-Fourth Annual Fall Clinical Conference of the Kansas City Southwest Clinical Society will occur October 7–10, 1946, at the Municipal Auditorium, Kansas City, Mo. Among the speakers at the sessions will be Dr. Charles A. Doan, F.A.C.P., Columbus, Ohio; Dr. Tinsley R. Harrison, F.A.C.P., Dallas, Tex.; and Walter L. Palmer, F.A.C.P., Chicago, Ill.

Dr. Edwin C. Swift, F.A.C.P., Jacksonville, has been elected Vice President of the Florida Medical Association.

Dr. Benjamin B. Souster, F.A.C.P., St. Paul, Minn., has become Secretary of the Minnesota State Medical Association.

Dr. James B. Bullitt, F.A.C.P., Chapel Hill, retired on June 5 from the faculty of the University of North Carolina School of Medicine. Dr. Bullitt was a member of the faculty for thirty-three years.

Dr. Morgan Cutts, F.A.C.P., Providence, has been elected Secretary of the Rhode Island Medical Society.

The American Public Health Association has announced the formation of a Committee to recommend awards for outstanding achievements in research and in the application of research dealing with diseases which constitute the major causes of death. The awards will be made available by the Albert B. and Mary Lasker Foundation. Each year the awards will consist of four gifts of $1000 and commemorative statuettes; especially significant contributions will be acknowledged by an additional award of $2500. The Committee includes the following Fellows of the College: Dr. George Baehr, Dr. Robert F. Loeb, Dr. Hugh R. Leavell, all of New York; Dr. Thomas Parran, Washington; Dr. James S. Simmons, Boston.

In the July News Notes, the rank at time of separation from service of Dr. Horst A. Agerty was incorrectly given as 'Captain.' Dr. Agerty held the rank of 'Major' at time of separation.

Dr. J. A. C. Gray, F.A.C.P., New York, formerly commissioned in the Medical Corps, USNR, has accepted a commission in the Medical Corps of the USN.

The 1947 Assembly of the New Orleans Graduate Clinical Assembly will be held in the Municipal Auditorium, New Orleans, February 24–27, 1947.

Dr. John W. Ferree, F.AC.P., formerly of Indianapolis, has become Director of the Division of Education and Special Projects of the American Social Hygiene Association. Dr. Ferree's office is located at 1790 Broadway, New York, N. Y., and he will reside at 21 Guion St., Pleasantville, N. Y.

The 1946 Sessions of the Omaha Mid-West Clinical Society will occur October 28 to November 1, 1946, inclusive.

Dr. George Cupp Griffith, Lt. Comdr., (MC), USN, Ret'd., F.A.C.P., Philadelphia, has received the commendation of the Surgeon General of the U. S. Navy. The citation included the following statement:

"Exercising unusual professional skill and energy you were, in a large part, responsible for the efficient functioning of the rheumatic fever unit at the Naval Hospital, Corona, Calif."

Dr. Henry A. Schroeder, F.A.C.P., who recently was separated from the Naval Reserve, is now Associate Professor of Medicine at Washington University School of Medicine, and Assistant Visiting Physician at Barnes Hospital, St. Louis. He was formerly Associate of the Rockefeller Institute.

A.C.P. Postgraduate Courses Increase in Demand

Although the Committee on Postgraduate Courses has more than doubled the number of courses for the autumn of 1946, the demand continues to exceed the facilities. Already several courses are oversubscribed, namely:

Course No. 1—Internal Medicine—University of Pittsburgh School of Medicine
Course No. 2—Psychosomatic Medicine—University of Colorado School of Medicine
Course No. 8—Cardiology—Massachusetts General Hospital
Course No. 13—Cardiology—University of Michigan Medical School

At the date this news item is prepared, August 23, 1946, all other courses are open, although the registration is rapidly mounting. All members received copies of the Postgraduate Bulletin early in August. One should not delay to file application because it is believed that practically all courses will be filled to capacity.

The Committee on Postgraduate Courses is already working on the schedule of courses for the spring of 1947. The following courses appear on the proposed schedule and others will be added:

Cardiovascular Disease—Northwestern University, Chicago, Ill.—Dr. J. Roscoe Miller, F.A.C.P., Director
Cardiovascular Disease—Emory University School of Medicine, Atlanta, Ga.—Dr. Bruce Logue, F.A.C.P., Director
Internal Medicine—University of Cincinnati School of Medicine, Cincinnati, Ohio—Dr. M. A. Blankenhorn, F.A.C.P., Director
Physical Medicine—University of Pennsylvania, Philadelphia, Pa.—Dr. George Morris Piersol
Tissue Growth and Tumors—Wanamaker Foundation, Lankenau Hospital, Philadelphia, Pa.—Dr. Stanley Reimann, F.A.C.P. and Dr. Edward L. Bortz, F.A.C.P., Directors

Still other courses under consideration include Diseases of the Chest, Neuropsychiatry, Pathology, Peripheral Vascular Diseases, and additional courses in Internal Medicine.

Copies of the Postgraduate Bulletin for Autumn 1946 Courses and for Spring 1947 are or will be obtainable by request to the Executive Secretary, American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

Retirements from Service

Since the last publication of this journal, the following members of the College have been reported retired or on terminal leave (to August 12, 1946 inclusive).

Stanton T. Allison, New York, N. Y. (Capt., MC, USNR)

John H. Baird, Washington, D. C. (Col., MC, AUS)
Lyle A. Baker, Hines, Ill. (Lt. Col., MC, AUS)
Roland W. Banks, Yeadon, Pa. (Major, MC, AUS)
Walter M. Bartlett, Benton Harbor, Mich. (Col., MC, AUS)

Gerald Blankfort, Little Rock, Ark. (Major, MC, AUS)
James E. Bovaird, Wolfeboro, N. H. (Capt., MC, AUS)
Norman H. Boyer, Boston, Mass. (Capt., MC, AUS)
Stewart F. Brewen, Wormleysburg, Pa. (Capt., MC, AUS)
Timothy F. Brewer, Hartford, Conn. (Lt. Comdr., MC, USNR)
Paul H. Burgert, Lake Forest, Ill. (Capt., MC, AUS)

Henry Caplan, Meriden, Conn. (Capt., MC, AUS)
William Chester, Mamaroneck, N. Y. (Lt. Col., MC, AUS)
Henry L. Cooper, Denver, Colo. (Major, MC, AUS)
William D. Coventry, Duluth, Minn. (Major, MC, AUS)

Worth B. Daniels, Washington, D. C. (Col., MC, AUS)
Thomas H. DeLaureal, Lake Charles, La. (Major, MC, AUS)

Robert W. Elliott, St. Louis, Mo. (Major, MC, AUS)
Clayton B. Ethridge, Washington, D. C. (Lt. Comdr., MC, USNR)

Thomas J. Fatherree, Soap Lake, Wash. (Comdr., MC, USNR)
Lucian M. Ferris, Vicksburg, Miss. (Lt. Col., MC, AUS)
Elmer Friedland, Buffalo, N. Y. (Major, MC, AUS)

J. Richard Gott, Jr., Murfreesboro, Tenn. (Comdr., MC, USNR)

Paul V. Hamilton, Cincinnati, Ohio (Lt. Col., MC, AUS)
Robert M. Harris, Miami, Fla. (Comdr., MC, USNR)
Thomas G. Hobbs, Chicago, Ill. (Major, MC, AUS)
Joseph F. Hughes, Philadelphia, Pa. (Comdr., MC, USNR)

Archibald D. Kennedy, Louisville, Ky. (Major, MC, AUS)
J. Allen Kennedy, Nashville, Tenn. (Major, MC, AUS)
Richard J. Kilhullen, Wilkes-Barre, Pa. (Major, MC, AUS)
Joseph R. Kriz, New Orleans, La. (Col., MC, AUS)

Howard J. Lee, Oshkosh, Wis. (Lt. Col., MC, AUS)
Jerome S. Levy, Little Rock, Ark. (Lt. Col., MC, AUS)
Philip H. Livingston, Chattanooga, Tenn. (Lt. Col., MC, AUS)
Louis Lowenstein, Montreal, Que., Can. (Wing Comdr., RCAF)
Joseph M. Lubitz, Chicago, Ill. (Lt. Comdr., USPHS (R))
Edgar H. Lutz, Montrose, Pa. (Capt., MC, AUS)

A. Seldon Mann, Alton, Ill. (Lt. Col., MC, AUS)
Donald F. Marion, Detroit, Mich. (Lt. Col., MC, AUS)
George C. McEachern, Forest Hills, N. Y. (Lt. Col., MC, AUS)
Harold P. McGan, Albany, N. Y. (Lt. Col., MC, AUS)
James A. McLaughlin, Ocean Bluff, Mass. (Lt., MC, USNR)
Robert J. Mearin, Syracuse, N. Y. (Lt. Comdr., MC, USNR)
Ralph W. Mendelson, Albuquerque, N. M. (Lt. Col., MC, AUS)
Frank Meyers, Buffalo, N. Y. (Lt. Col., MC, AUS)
Saul Michalover, Brooklyn, N. Y. (Col., MC, AUS)

Walter C. Nalty, Fort Bayard, N. M. (Lt. Col., MC, AUS)
Jack C. Norris, Atlanta, Ga. (Capt., MC, USNR)

Abraham Penner, New York, N. Y. (Lt. Col., MC, AUS)
Thornton T. Perry, III, Rochester, Minn. (Lt., MC, AUS)
Lee T. Pruit, Beaumont, Tex. (Col., MC, AUS)

Alexander Sanders, Chicago, Ill. (Major, MC, AUS)
Henry A. Schroeder, New York, N. Y. (Comdr., MC, USNR)
George Schwartz, New York, N. Y. (Capt., MC, AUS)
J. Dunbar Shields, Jr., Concord, N. H. (Lt., MC, USNR)
Donald G. Stannus, Miami Beach, Fla. (Major, MC, AUS)
Irwin D. Stein, Mt. Vernon, N. Y. (Capt., MC, AUS)
Charles F. Sweigert, San Francisco, Calif. (Lt. Col., MC, AUS)

David S. Traub, Louisville, Ky. (Capt., MC, AUS)

Robert A. Ullman, Buffalo, N. Y. (Capt., MC, AUS)

Stoughton R. Vogel, Philadelphia, Pa. (Major, MC, AUS)
William von Stein, New York, N. Y. (Major, MC, AUS)

Richard Wagner, Elizabeth, N. J. (Capt., MC., AUS)
Edmund F. Walker, Worcester, Mass. (Major, MC, AUS)
Edgar Wayburn, San Francisco, Calif. (Major, MC, AUS)
Zolton T. Wirtschafter, Cleveland, Ohio (Lt. Col., MC, AUS)

Ellis W. Young, Pittsburgh, Pa. (Capt., MC, AUS)

MINUTES OF THE BOARD OF REGENTS

PHILADELPHIA, PA.

MAY 12, 1946

The first meeting of the Board of Regents during the Philadelphia Annual Session was held at Convention Hall, Sunday, May 12, 1946, at two o'clock, with the President, Dr. Ernest E. Irons, presiding, Mr. E. R. Loveland acting as Secretary, and with the following in attendance:

Doctors David P. Barr; William D. Stroud; James J. Waring; George Morris Piersol; Christopher C. Shaw; T. Homer Coffen; Jonathan C. Meakins; Hugh J. Morgan; Francis G. Blake; James F. Churchill; Reginald Fitz; Roger I. Lee; Charles T. Stone; Walter B. Martin; William S. Middleton; James E. Paullin; LeRoy H. Sloan; George F. Strong; Chauncey W. Dowden; Paul W. Clough; Major General Norman T. Kirk, Surgeon General, U. S. Army; Capt. Howard H. Montgomery, representing the Surgeon General, U. S. Navy.

By resolution, the Board of Regents dispensed with the reading of the minutes of the preceding meeting but accepted them as published in a recent issue of the Annals of Internal Medicine.

The President called upon the Secretary to present communications, which were as follows:

1. A letter enclosing a contribution of $10,000 from Dr. James D. Bruce, Ann Arbor, Michigan, for the founding of a memorial award to the late Alfred Stengel, "one of the real founders of the College as we know it."

One-half of the award is to be allocated to an annual lecture or award, designating it as the appropriate committee may see fit, to the cause of preventive medicine. Dr. Bruce further specified:

"There are a number of approaches to our educational problems which I shall hope to take up later. One thing that I wish to have understood at this time is that the acceptance of this, or further contributions, involves no obligation on the part of the College to accept any suggestions that I may make. In other words, these contributions are to be used in accordance with the ideals and purposes of the College.

"The magnificent contribution of the College during the war has added to its prestige and further demonstrated the wider rôle it must and eventually will play in medical education. Its policy and activities in this field have been soundly based, and at this time it seems to me that efforts to enlarge these along proved lines would gradually lead to greater usefulness. It has been my hope to assist from time to time with the financial burden, and as a beginning of a fund within the endowment, I should like to make a contribution in the amount of $10,000, which would permit the establishment of two lectureships or awards. This, together with future amounts which I hope to send from time to time, while kept together as one fund, will be included in the endowment and the income used in accordance with the present policies of the College.

"The policy in the educational field, as I understand it, is to devote these funds to research, scholarships, lectureships, and awards, as well as to the growing responsibility in the postgraduate field."

On motion by Dr. Lee, seconded by Dr. Paullin, it was resolved that the Board of Regents accept this magnificent gift with deep appreciation, and that the President and Secretary General shall confer with the Committee on Fellowships and Awards for the setting up of the Bruce Fund and the setting up of policies and principles regarding its use.

2. A communication from Dr. F. F. Borzell, Chairman of the Wartime Graduate Medical Meetings Committee, in which Dr. Borzell proposed to present to the American College of Physicians office equipment valued at $288.52, and accompanying his letter was a check for $397.95, the proportional balance remaining in the treasury from former contributions made by the College.

Dr. Borzell further presented final reports in all detail of the work of the Committee on War-time Graduate Medical Meetings, for filing in the College archives.

A resolution was adopted providing that the report be accepted and filed, and the Board of Regents express to Dr. Borzell and his associates its commendation and appreciation for the magnificent work performed, and also extend its thanks to the committee for the gift of the furniture and equipment and the refund of remaining proportionate fees.

3. A communication from Dr. E. D. Hitchcock, College Governor for Montana, embracing the following resolution adopted at a regional meeting of the College on April 27, 1946, for the combined states of Montana and Wyoming:

"Resolved, that we request the Board of Governors of the American College of Physicians to unite Montana and Wyoming under a single Governorship for purposes of administration.

"Be it further resolved, that this union be continued until such time as Wyoming is able to qualify under a separate state."

After discussion, a resolution by the Board of Regents was adopted authorizing the President to appoint a Governor to serve for both states.

4. A communication from W. C. Mennecke, Secretary, University of Chicago Board of Trustees, acknowledging receipt of $1,062.40, proceeds from a postgraduate course given for the College at the University of Chicago last autumn, said fund having been used in support of a fellowship in gastroenterology.

This communication was an expression of appreciation for generous assistance from the College.

5. A communication from members of the College in Western Michigan, who on March 20, 1946, at Muskegon, organized a regional group of the American College of Physicians "to promote friendship and understanding among the Fellows and Associates in Western Michigan, and to foster scientific investigation in the field of internal medicine."

6. The next communication was a report prepared by the Executive Secretary, the Educational Director, the Secretary General, the Treasurer, and the Chairman of the Committee on Graduate Courses, as follows:

Program of Postgraduate Courses and the GI Bill of Rights

"The postgraduate courses sponsored by the American College of Physicians are organized primarily for Fellows and Associates of the College. Some non-members may be accommodated when facilities permit, but in the majority of courses, all places are taken by members.

"During the period of World War II, the College charged no tuition fee to any medical officer on active duty or on terminal leave. This courtesy was extended to members and non-members alike. With the termination of the war, and the increased demand for the College courses, our facilities have been taxed to the maximum, with the result that a much smaller number of non-members can be accommodated. In fact, facilities in some courses are inadequate for the member demand.

"The College will be unable to provide veteran medical officers, members or non-members of the College, the benefits of the amended GI Bill of Rights, through which the Veterans Administration would pay tuition fees of medical veterans pursuing its courses. The College has not the administrative machinery to comply with the various and complex regulations through which collections must be made through the Veterans Administration.

"Furthermore, it is believed that the legislators who formulated the original training program for veterans did not have in mind the short one, two or three weeks courses, such as provided by this College. Fees for College courses are comparatively small; all such fees are turned over to the director or institution where a College course is given; the College underwrites all other expenses of promotion, advertising, printing and registration.

"The College regrets its inability, at this time, financially and administratively, to launch upon a program of training for medical veterans, through the Veterans Administration, but will accommodate as many as possible who wish to register in the regular manner."

On resolution unanimously carried, the report was approved.

7. A communication from Dr. Manfred Kraemer of Newark was presented in which the writer decried the use of questions on proposal forms which refer to the candidate's race or religion. The letter was referred to the Credentials Committee after discussion by the Board as a whole.

8. A communication from Dr. Reginald Fitz, Official College Marshal, in which Dr. Fitz desired to retire. The Board of Regents unanimously voted that he should continue this work, especially in view of the fact that it considers no one else so adequately qualified.

9. A communication from Dr. Barnett Greenhouse, F.A.C.P., to Dr. Francis G. Blake, Regent, containing a resolution purporting to correct an embarrassing situation now existing between the American College of Physicians and the American Board of Internal Medicine.

10. A communication from the American Board of Internal Medicine notifying the Board of Regents that certain appointments to the American Board of Internal Medicine will have to be made to fill vacancies which will occur on June 30, 1946.

DR. FITZ: Mr. Chairman, Dr. Waring has been designated Chairman of the American Board of Internal Medicine.

DR. WARING: There are two matters I am instructed to bring to your attention. The first is that the Board would like to increase its membership from nine to twelve

members. This is a necessity because of the very large amount of work to be done, devolving so heavily upon the members of the Board. There should be seven appointees instead of five from the American College of Physicians; five appointees from the Section on Medicine of the American Medical Association, instead of three. We would like to have a panel of names presented and one name will be chosen from that panel to succeed Dr. G. Gill Richards who retires, and two will be added to the list. May I also suggest that when the selection is finally made, notification shall come from the Secretary of the American Board of Internal Medicine.

CHAIRMAN IRONS: I take it that this is largely for the information of the Board of Regents at this time and that it will be acted upon by this Board at its meeting on Friday of this week.

REPORT OF THE SECRETARY GENERAL

DR. GEORGE MORRIS PIERSOL

DR. PIERSOL: The Secretary General wishes to report the deaths of 44 Fellows and 5 Associates since the last meeting of this Board, as follows:

Fellows

Angle, Fred Ernest	Kansas City, Kan.	October 29, 1945
Bartlett, Frank Herbert, Jr.	Muskegon, Mich.	January 25, 1946
Black, Benjamin Warren	Oakland, Calif.	December 1, 1945
Blackford, John Minor	Seattle, Wash.	September 12, 1945
Brasted, Howard Spencer	Hornell, N. Y.	August 28, 1945
Brown, Frederick Lane	New Brunswick, N. J.	January 30, 1946
Brown, Gilbert T.	Dayton, Ohio	November 17, 1945
Carter, Larue D.	Indianapolis, Ind.	January 22, 1946
Evans, Newton	South Pasadena, Calif.	December 19, 1945
Frissell, Lewis Fox	New York, N. Y.	October 24, 1943
Fuller, Frank M.	Keokuk, Iowa	March 19, 1946
Gardner, Edwin Leslie	Minneapolis, Minn.	January 29, 1946
Gober, Olin F.	Temple, Tex.	January 26, 1946
Hallett, Harley James	M.C., U. S. Army	December 11, 1945
Hamman, Louis	Baltimore, Md.	April 28, 1946
Hanes, Frederic Moir	Durham, N. C.	March 25, 1946
Holtzapple, George E.	York, Pa.	February 22, 1946
Hyde, Clarence L.	Akron, Ohio	December 1, 1945
Jennings, Alpheus F.	Detroit, Mich.	November 16, 1945
Jordan, Ferdinand M.	White Plains, N. Y.	August 14, 1945
Kibler, Charles S.	Tucson, Ariz.	February 25, 1946
Lamson, Robert Ward	Los Angeles, Calif.	January 6, 1946
Leathers, Waller S.	Nashville, Tenn.	January 26, 1946
Lowe, Donald Blair	Akron, Ohio	March 2, 1946
Lowry, Tom	Oklahoma City, Okla.	December 11, 1945
Mannheimer, George	New York, N. Y.	December 10, 1945
Manning, Isaac Hall	Chapel Hill, N. C.	February 12, 1946
Matson, Ralph Charles	Portland, Ore.	October 26, 1945
Mercer, Clifford David	West Union, Iowa	December 25, 1945
Mills, Charles W.	Tucson, Ariz.	September 29, 1945
Moore, Alexander B.	Washington, D. C.	March 8, 1946
Palmer, Harold Dean	Philadelphia, Pa.	November 20, 1945

Pierson, Philip Hale	San Francisco, Calif.	January 17, 1946
Ramirez, Maximilian A.	New York, N. Y.	March 4, 1946
Rigney, Lawrence J.	Wilmington, Del.	November 28, 1945
Robertson, Harold E.	Rochester, Minn.	March 8, 1946
Rosamond, Eugene	Memphis, Tenn.	December 12, 1945
Smith, Archibald D.	Garden City, N. Y.	November 22, 1945
Smith, Fred M.	Iowa City, Iowa	February 23, 1946
Stookey, Paul Forrey	Kansas City, Mo.	November 25, 1945
Sturtevant, Mills	New York, N. Y.	October 29, 1945
Trasoff, Abraham	Philadelphia, Pa.	November 24, 1945
Way, Charles T.	Cleveland, Ohio	February 4, 1946
Wright, George Jesse	Pittsburgh, Pa.	October 1, 1945

Associates

Glenn, Paul Mitchell	Cleveland, Ohio	December 21, 1945
Jenny, Thomas Gotthart	Miami, Fla.	August 31, 1945
Jones, Howard	Circleville, Ohio	December 12, 1945
Kugel, Maurice Alexander	Miami Beach, Fla.	March 9, 1946
Marsh, Van Newhall	Talmage, Calif.	July 25, 1945

Since the last meeting of this Board, 88 new Life Members have been added, making a grand total of 488, of whom 40 are deceased, leaving a balance of 448. They are as follows:

Seymour H. Silvers	Brooklyn, N. Y.
Samuel Nesbitt	Arlington, Va.
Elmer E. Glenn	Springfield, Mo.
Wilton Ross Glenney	Pottsville, Pa.
David W. Carter, Jr.	Dallas, Tex.
James F. Slowey	Cleveland, Ohio
Irving Gray	Brooklyn, N. Y.
William M. LeFevre	Muskegon, Mich.
Albert T. Leatherbarrow	Hampton Station, N.B., Can.
Allen H. Bunce	Atlanta, Ga.
Charles T. Stone	Galveston, Tex.
David B. Flavan	St. Louis, Mo.
David W. Kramer	Philadelphia, Pa.
George H. Anderson	Spokane, Wash.
Orange Van Calhoun	Lincoln, Nebr.
W. W. Alexander	Florence, Ala.
Harold W. Gregg	Butte, Mont.
Jacob S. Blumenthal	Minneapolis, Minn.
Frank G. LeFor	Yakima, Wash.
George Tryon Harding, III	Columbus, Ohio
John Francis Briggs	St. Paul, Minn.
Barnet P. Stivelman	New York, N. Y.
Louis L. Perkel	Jersey City, N. J.
Edward James Lynch	Shelton, Conn.
George C. Mackie	Wake Forest, N. C.
Charles H. Harrell	Norfolk, Va.
Harold L. Amoss	Greenwich, Conn.
William G. Gardiner	Toledo, Ohio
Murray Eugene Goodrich	Toledo, Ohio
Francis F. Borzell	Philadelphia, Pa.

Stanley Erwin	Jacksonville, Fla.
Andrew C. Ivy	Chicago, Ill.
Frank R. Menagh	Detroit, Mich.
Benjamin F. Wolverton	Cedar Rapids, Iowa
Harold E. Waxman	Pittsburgh, Pa.
Burton E. Hamilton	Boston, Mass.
Robert W. Blumenthal	Milwaukee, Wis.
Henry J. Ullmann	Santa Barbara, Calif.
Frank J. Montrose	Buffalo, N. Y.
Thomas P. Sharkey	Dayton, Ohio
Clapham P. King	Washington, D. C.
Joseph Emile Blum, Jr.	Greenwell Springs, La.
Edmond Michael Walsh	Omaha, Nebr.
L. Carl Sanders	Memphis, Tenn.
Harry L. Arnold, Jr.	Honolulu, T. H.
Edward Saunders Dillon	Philadelphia, Pa.
Everett C. Jessup	Roslyn, N. Y.
Frank L. Williman	Washington, D. C.
John L. Kleinheksel	Wichita, Kan.
Paul D. White	Boston, Mass.
Daniel L. Sexton	St. Louis, Mo.
Henry H. Turner	Oklahoma City, Okla.
Russell S. Boles	Philadelphia, Pa.
Douglas Deeds	Denver, Colo.
Titus Holliday Harris	Galveston, Tex.
Ernest L. MacQuiddy	Omaha, Nebr.
Treacy H. Duerfeldt	Tacoma, Wash.
Paul V. Ledbetter	Houston, Tex.
Frank R. Mount	Portland, Ore.
K. W. Benson	Berkeley, Calif.
Henry N. Leopold	San Antonio, Tex.
Archie Marvin Roberts	Los Angeles, Calif.
Henry R. Carstens	Philadelphia, Pa.
J. Sudler Hood	Clearwater, Fla.
Eugene Fagan Traut	Oak Park, Ill.
Kenneth S. Davis	Los Angeles, Calif.
Oscar B. Hunter	Washington, D. C.
James Burnett Shields	Glens Falls, N. Y.
Earl C. Waterbury	Newburgh, N. Y.
Lorenz W. Frank	Denver, Colo.
Harold L. Tonkin	Williamsport, Pa.
Will S. Horn	Fort Worth, Tex.
William C. Blake	Tampa, Fla.
Lawrence C. Towne	Lansing, Mich.
William R. Vis	Grand Rapids, Mich.
William C. Nichols	Fargo, N. D.
Henry C. Gotshalk	Honolulu, T. H.
Lawrence Arthur Williams	Pasadena, Calif.
Virgil G. Presson	Tucson, Ariz.
Alfred W. Dubbs	Allentown, Pa.
Gertrude M. Engbring	Chicago, Ill.
Howard Wakefield	Chicago, Ill.
John J. Dumphy	Worcester, Mass.

Robert Stanley Flinn	Phoenix, Ariz.
James J. Waring	Denver, Colo.
John W. Shuman	Santa Monica, Calif.
J. W. MacIntosh	Halifax, N. S., Can.
Samuel M. Poindexter	Boise, Idaho

CHAIRMAN IRONS: The report of the Secretary General will be received and recorded.

NEW BUSINESS AND REPORTS

DR. PIERSOL: The Committee on Credentials has held two meetings since the last meeting of the Board of Regents—April 14, 1946, and May 12, 1946.

Among communications was one concerning an Advisory Committee in the Brooklyn area to serve with the College Governor for Eastern New York in reviewing candidates. Letters were received from Doctors George E. Anderson, Frank Bethel Cross, Irving J. Sands, and covering letters from Governor Asa L. Lincoln. The Committee on Credentials expressed full agreement and approval of a Brooklyn Advisory Committee. It was the advice of the Committee, however, that there should be no official connection between this Advisory Committee and the Brooklyn Society of Internal Medicine. Governor Lincoln is fully authorized to select an Advisory Committee and to record the names in the executive offices of the College.

Applications for reinstatement to Fellowship.

1. The reinstatement to Fellowship of a former member who is now the dean of an unapproved medical school, against which an injunction is now pending, was not approved by this Committee.

2. Dr. Reuben A. MacBrayer, Fayetteville, North Carolina; his reinstatement is approved by the Credentials Committee with the recommendation that the Board of Regents formally reinstate him on May 12, 1946.

Candidates for Fellowship.

The following is a summary of the recommendations of the Committee (meeting of April 14, 1946):

Recommended for Advancement to Fellowship	35	
Recommended for Election Directly to Fellowship	17	52
Recommended for Election first to Associateship		3*
Deferred		13
Rejected		5
		73

Candidates for Associateship.

The following is a summary of the recommendations of the Committee:

Recommended for Election	111
*Fellowship Candidates Recommended for Election first to Associateship	3*
Deferred	6
Rejected	55
	172
*plus	3

A full list of the names of candidates recommended for election to Fellowship and Associateship is included with the list reviewed this morning and later presented in this report for action.

The Committee records that it has recommended that proposals be withdrawn or rejected in numerous cases for the sole reason that said proposals have been on file for more than a year and the candidates, in many cases, have been on military service and have been unable yet to meet all the requirements; consequently, their biographical data become out of date and it is impractical to keep their old proposals on file. The sponsors of such candidates will be notified that this action has been taken without prejudice and that when the candidate is qualified, a new proposal should be submitted.

. . . Formal resolutions were adopted by the Board of Regents approving the recommendations of the Committee on Credentials, reinstating to Fellowship Dr. Reuben A. MacBrayer, Fayetteville, North Carolina, and approving the above report to this point. . . .

DR. PIERSOL (Continuing his report): The second meeting of this Committee was held this morning at 9:30. Several communications were discussed which contained nothing for action by the Regents. One of these inquiries was for the purpose of establishing what standing the College will accord to the "Certificate of Specialization" issued by the Royal College of Physicians of Canada. This is separate and distinct from certification by the Royal College. It does not represent anything comparable to certification, but merely indicates the specialty of the physician. Consequently, the Credentials Committee cannot accept it in lieu of formal certification by an American specialty board or the Royal College of Physicians of Canada.

The following is an analysis of the candidates for Fellowship and Associateship considered by the Committee today:

Candidates for Fellowship.

Recommended for Advancement to Fellowship	15	
Recommended for Election Directly to Fellowship	5	20
Recommended for Election First to Associateship		5*
Deferred		7
Rejected		6
		38

Candidates for Associateship.

Recommended for Election	85
*Fellowship Candidates Recommended for Election First to Associateship	5
Deferred	19
Rejected	7
	111
*plus	5

The Committee on Credentials, therefore, recommends to the Board of Regents the election to Fellowship of 72 candidates and the election to Assbciateship of 204 candidates.

. . . On resolution formally adopted, the following 72 candidates were elected to Fellowship: (This list was published in the June, 1946, issue of this journal.)

. . . On resolution formally adopted, the following 204 candidates were elected to Associateship: (This list was published in the June, 1946, issue of this journal.)

DR. PIERSOL (Continuing): The following is a report on the candidates elected to Associateship April 20, 1941, five years ago, whose terms now expire:

Already Advanced to Fellowship	65
Deceased	2
Dropped for failure to take up election	0
Rejected previously	1
Rejected today; credentials inadequate (Group A–2)	4
Dropped today; Failed to present credentials (Group B–2)	12
Dropped for Delinquency	0
Resigned	4
Missing in military action (Downs and Stoneburner)	2
Proposals for advancement outstanding (Group A–1)	18
Credentials not presented (Group B–1)	21
Total Candidates elected, 4/20/41	129

Group A. Proposals for advancement are on file for the following:

1. Military Officers; although these proposals are on file their advancement has been temporarily deferred for additional credentials, but since they are on military service, their time has been extended.

(Group of 18—Names not published)

2. Practicing Physicians; credentials presented but inadequate:

(Group of 4—Names not published.)

Group B. Associates who have not presented adequate (or no) credentials for Fellowship:

1. Military Officers, may have extension of time:

Agnor, Elbert Boogher, Atlanta, Ga. (AUS)
Burgeson, Paul Arthur, Warsaw, N. Y. (AUS)
Childs, Edward Patterson, New York, N. Y. (USNR)
Cummings, Hatch Whitfield, Houston, Tex. (USNR)
Dickey, Francis George, Baltimore, Md. (AUS)
Edwards, Robert Allison, Houston, Tex. (AUS)
Flickinger, Don Davis (MC, USA)
Green, Mervin Edward, Toledo, Ohio (AUS)
Hays, James Franklin (MC, USN)
Kimbrough, Robert Cooke, Jr., Ann Arbor, Mich. (AUS)
Kwitny, Isadore Jacob, Indianapolis, Ind. (AUS)
Lynch, George William, Boston, Mass. (USNR)
Osborne, John Randolph, Middletown, N. Y. (USNR)
Pritchett, Clark Poston, Columbus, Ohio (AUS)
Rastetter, Joseph Walter, Milwaukee, Wis. (USNR)
Reymont, Anthony Edward, Santa Fe, N. M. (USNR)
Rosenstiel, Henry Carl, Freeport, Ill. (AUS)
Schneierson, S. Stanley, New York, N. Y. (USNR)
Strauss, Arthur Simpson, White Plains, N. Y. (AUS)
Warr, Otis Sumter, Memphis, Tenn. (AUS)
Woods, Bertrand Odell, Portland, Ore. (AUS)

2. Practicing Physicians; must now be dropped:

(Group of 12—Names not published.)

Many of these (Group B–2) are very good men but the Committee has no choice if they fail to present their credentials within a period of five years, as specified by the By-laws. All of them have been notified and requested to submit their credentials on several occasions. They are now automatically dropped from the Roster.

. . . On motion, seconded and duly carried, the action of the Credentials Committee was approved and its report approved as a whole. . . .

CHAIRMAN IRONS: Next will be the report of the Committee on Survey, Dr. William S. Middleton, Chairman.

DR. MIDDLETON: Mr. Chairman, the Committee on Survey met on April 14, 1946, and offers the following recommendations relative to changes in the By-laws and regulations. Upon its careful study there were no deviations from the Constitution.

ARTICLE V

Election of Fellows

Section 1. A Fellow of the College shall have met the following qualifications and requirements:

(a) He shall have qualified and served a minimum period of three years as an Associate, except upon recommendation of the Committee on Credentials by reason of very special qualifications as hereinafter set forth.

(b) He shall have graduated from a medical school acceptable to the Board of Regents, at least five years prior to the time of his election, and if engaged in practice, his professional activity must be confined to the field of internal medicine or a related specialty.

(c) If he is not a bona fide teacher or permanent laboratory worker, he shall have been in the actual practice of internal medicine at a permanent location for at least three years preceding nomination for Fellowship.

(d) The criteria of eligibility for election to Fellowship are bi-lateral:

1. Detailed information concerning the candidate's hospital and academic appointments, with particular reference to the size and nature of the hospital service and the exact teaching responsibility; published contributions in media acceptable to the Committee on Credentials, with particular emphasis upon papers published during the period of Associateship; personal approval by Fellows in his territory, with reference to his character, ethical standing and medical activities; evidence of postgraduate training and attendance upon the Annual Meetings of the College.

2. He shall be certified by the recognized national board of certification in his particular field, where such an accrediting board exists. This regulation, however, shall not apply to candidates who were elected to Associateship prior to April 6, 1940, nor to candidates from the Army, Navy and Public Health Services who were elected prior to and including April 1, 1944.

PROPOSAL

Section 2. His name shall be proposed in writing by a Master or Fellow of the College from the same state, province, or territory, not an officer or member of the Board of Regents; he shall be seconded by another Master or Fellow from the same state, province or territory and endorsed by the member of the Board of Governors

from the state, province or territory in which he resides, or by the Surgeon General of the Army, Navy or Public Health Service of which he is a member, or by an Officer of the College or by a member of the Board of Regents. His nomination must be accompanied by a written statement made both by the proposer and the seconder, containing all of the above cited qualifications of the candidate. Further, the name of the candidate shall be sent to each Fellow in the candidate's locality with the request for comments as to the candidate's fitness. The proposer must be prepared, moreover, to add such further information as may be requested by the Committee on Credentials.

Successful candidates shall be so notified immediately after their election and shall be urged to attend the next succeeding Convocation, when Fellowships will be formally conferred. The official Fellowship Certificate, signed by the President and the Secretary General, shall be issued following the Convocation. Acknowledgment of its receipt shall be made upon an official card, signed and dated by the newly elected Fellow, and returned to the Executive Secretary, to be added to the official College roll.

Section 3. Proposals for direct election to Fellowship, with or without prior certification by the appropriate certifying board, may be made to the Committee on Credentials. This manner of election is an unusual mark of distinction; hence such candidates must be preëminent in teaching, research or clinical practice. In advancing individuals for such consideration, the following details must be furthermore considered: maturity, national reputation, publications and other contributions to medical science and public welfare. It is obvious that the Committee on Credentials will exercise due discrimination in all proposals for direct election to Fellowship. For this reason, complete data concerning the candidate and his activities must accompany the proposal.

This ruling will not be invoked for candidates who have failed of regular advancement from Associateship to Fellowship.

Article VI

(new article)

Election of Masters

Section 1. A special committee on Masterships will be named by the Persident. This committee will consist of two members from the Board of Regents and one member from the Board of Governors. It will bring its nominations of Masters to the Board of Regents for election.

Article VII

(Replacing Article VI)

Section 1. An Associate of the College shall have met the following qualifications and requirements:

(a) He shall hold the degree of M.D., M.B., or M.D., C.M., from a medical school acceptable to the Board of Regents.

(b) If engaged in the practice of medicine, the candidate, after receiving his degree, shall have had at least one year of internship in an approved hospital and three years of graduate training in internal medicine or allied fields. One year of this graduate training may be spent in the basic sciences. By an alternative plan, instead of an organized system of graduate training such as is afforded by a residency or fellowship, a candidate may satisfy this requirement under the preceptorship

of a recognized specialist approved by the American Board of Internal Medicine or a similar certifying Board, after conference with the Committee on Credentials. Such opportunities must be approved by the American College of Physicians prior to their acceptance in lieu of the conventional graduate training. Under no circumstances can this plan be made retroactive.

(c) He shall be a member in good standing in his local, state, provincial or territorial and national medical societies, except in the case of those not engaged in practice, such as full-time teachers, research workers, those holding official hospital positions, etc.

(d) If a practitioner, he shall be licensed to practice medicine in his state, province or territory, and shall indicate his purpose to practice internal medicine from the date of his application, or be a Medical Officer in the Government Service, either in the United States or the Dominion of Canada, in American or Foreign Service. If not a practitioner, he shall hold an official institutional position in one of the allied branches of internal medicine or in medical research.

PROPOSAL

Section 2. His name shall be proposed on the official blank of the College by a Master or Fellow residing in the same state, province or territory, not an Officer or member of the Board of Regents; he shall be seconded by another Master or Fellow also from the same state, province or territory, and endorsed by the member of the Board of Governors from the state, province or territory in which he resides, or by the Surgeon General of the Army, Navy or Public Health Service, of which he is a member, or in special instances, by an Officer of the College or by a member of the Board of Regents.

The credentials of candidates for Associateship shall be considered first by the Committee on Credentials, which Committee shall report to the Board of Regents for election or rejection.

Successful candidates shall receive at once, from the Board of Regents through the Executive Secretary, an appropriate official notification of their election to Associateship in the College.

TERM OF ASSOCIATESHIP AND ELIGIBILITY FOR FELLOWSHIP

Section 3. Candidates so elected shall be continued as Associates for a term not to exceed five years.

Such Associates shall be eligible for election to Fellowship at the end of three years after election to Associateship. Upon expiration of this three year period he shall be notified in writing by the Committee on Credentials of his eligibility for election to Fellowship during the next two years, provided he shall have met within that time the requirements necessary for Fellowship. If not elected to Fellowship within five years, his Associateship automatically ceases.

CHAIRMAN IRONS: Perhaps Dr. Middleton will explain to us in what respects this makes changes in the present By-laws.

DR. MIDDLETON: The present By-laws are modified in only a few respects. The Committee was charged with the responsibility of clarifying the circumstances of certification by the American Board of Internal Medicine. There had been a general disapproval among the Board of Governors relative to certification being a prerequisite for admission to Associateship. That position was sustained unanimously by the Survey Committee. It felt that while it is a great step in the evolution of the training of a man for Fellowship, certification should not be a barrier to his entrance upon the responsibilities of Associateship, which in a sense is merely a probationary term before the candidate advances to the maturity of Fellowship.

The proper implementation of the preceptorship into a system whereby the American College of Physicians could participate with the American Board of Internal Medicine in the recognition of exposures other than ordinary residencies and fellowships might be a very important link. It was suggested by Dr. Meakins in the American Board of Internal Medicine that these preceptorships offer to many young men opportunities that are at least as good as the educational outlet of a residency; accordingly, it was deemed wise that the American College of Physicians enter into a reciprocal relation with the American Board of Internal Medicine in recognizing preceptorship as a stage in development.

If we are going to hold to the standards of admission to Fellowship, there should not be erected between the College and the American Board—one a rating group and the other a qualifying group for Fellowship—such a barrier that it cannot be surmounted by an individual who answers one and yet, because of the strictures of the other, is forbidden Fellowship in the American College of Physicians.

In effect, there are only two major changes—one having to do with the requirement of certification by the American Board of Internal Medicine, or a similar certifying Board, for advancement to Fellowship, rather than to the earlier suggestion of certification as a prerequisite for Associateship; and the second, the preceptorial plan as implementing training for the men who perhaps prefer the preceptorial plan to a residency or fellowship. The small third item of change is purely a geographic one—meaning that a candidate's sponsors shall come from the same state, province or territory in which the candidate resides.

I believe provision should also be made for candidates from Mexico and Central American States. While it has been customary to accept candidates from any part of North America or any of its dependencies, there is nothing in the Constitution that admits it.

DR. MEAKINS: I should think that Newfoundland, Greenland and even Iceland would be included also in North America. The Committee will want to consider all the geographic possibilities.

DR. DOWDEN: Mr. Chairman, I understand a candidate is not eligible for Associateship until three years after he has graduated. Then there is a five year period of Associateship during which he must qualify for Fellowship, although he may present his credentials in three years. There are at least six years after graduation before he is eligible to take the examinations of his specialty Board. Consequently, the date of his eligibility for Fellowship and his eligibility to take the Board examinations is the same—two periods of three years each. Is that correct, Dr. Middleton?

DR. MIDDLETON: Exactly. In other words, he cannot take the Board of Internal Medicine examinations until five years after his first year of internship.

DR. LEE: Mr. President, I am going to suggest that this ought to be referred to the Board of Governors because that Board is a little bit closer to the incoming Associates and Fellows and I think before we pass upon this matter, it should be referred to the Board of Governors for their comments; therefore, I move that this be referred to the Board of Governors for any comments that they may make and that it then be returned to this Board for action, but no action be taken at this time.

. . . The motion was seconded by Dr. Stroud and carried. . . .

DR. WARING: I should like to discuss the matter of preceptorships in the American Board of Internal Medicine. Last night the Board had a very thorough discussion upon this matter especially with regard to the difficulty of passing judgment and approval upon men applying as preceptors. We came to the conclusion that because of these difficulties it would be wise to do away entirely with preceptorships and the unanimous decision was that as of July 1, 1947, all preceptorships shall end. Between now and then the Board will take no new preceptors.

DR. MIDDLETON: I am very sorry to hear this. I believe it to be a backward step, if I may say so. I dislike to see the time pass when eminent teachers and clinicians may have in their offices young men coming into the field of internal medicine by reason of exposures that are highly advantageous from an educational standpoint. I agree, the difficulties of control are obvious. The Board had an earlier expedient to tell just how good these exposures proved to be by the result of particular training. A candidate or two from a preceptor in a community in which the Board was in doubt, would very shortly reflect the adequacy or inadequacy of his training when he came up for examination. I believe there are two particular ends, educationally, that we are meeting here. First, the end of the men who need training; the inability of our educational institutions; the other end of a type of probationship that the man goes through as a house fellow after the earlier period, living in the very atmosphere of medicine, whether it is the hurly-burly daily practice, or the office or the clinic, that cannot possibly be replaced by the large organized educational program of a general hospital.

DR. WARING: It has seemed to members of the American Board of Internal Medicine that preceptorship is becoming a matter whereby a young man goes into an older doctor's office, does much of his hack work for him, makes his night calls and some of his other less attractive calls and there is little actual definite supervision of his work. It is for that reason that the Board decided that the preceptorship plan is difficult of appraisal in the first place, and the number of applications as preceptors has increased very greatly.

CHAIRMAN IRONS: The Chairman is fully in accord with Dr. Middleton. We shall bow to the feeling of the Board. There simply are not the opportunities available in this country for all of the men who want this kind of training. I agree, it is tremendously difficult to evaluate these preceptorships, but just the same, it does seem that men with proper preceptors can get much valuable training.

DR. BARR: Does this action of the Board of Internal Medicine mean that it will not accept training by men they think can give training, or that the Board has ceased to recognize officially and permanently a certain list of preceptors?

DR. WARING: The American Board has a list of 25 or 30 preceptors recognized to date; any young men working under these are approved, after a certain number of years, as meeting certain requirements of the Board. The American Board has carefully reviewed its list of preceptors; certain of them do not meet the requirements fairly; the Board knows from personal experience that the training being given to some of the young men under some of these preceptors is inadequate from the Board's standpoint. Because of the great difficulty in passing on all the additional applications of preceptors and because of certain inadequacies among the present list, the Board decided that the present preceptors shall function until July 1, 1947; that in the interval the Board will recognize no other preceptors; that after July 1, 1947, there will be no further recognized preceptors. I agree with the Chairman that there are many men that could meet these requirements, but the difficulty of being sure about them, the difficulty of refusing one or another doctor as a preceptor seems almost insurmountable.

DR. MEAKINS: Mr. Chairman, in speaking of this matter I think we have to be realistic as to where these men are going to obtain three years of residency in hospitals in North America. They may obtain it at a teaching hospital but there are very few who after their junior internships can go on for three years. The openings just don't exist in a teaching hospital. If it is in a non-teaching hospital, what guarantee has the American Board of Internal Medicine that just three years in any hospital is going to be efficient training? There are hospitals and hospitals. In some of them the training is bad and it should never be accepted. Furthermore, some years ago we visualized that a man might go to Europe and take his training

there. This, of course, has not been possible for the last few years. Now, to make up for this gap, which I think is a very real gap, a good resident training in the hospitals of North America, we visualize the possibility of a few men taking these young candidates, not as slaves, not as night workers, but for real training. I don't think the list of preceptors should be 42; I would reduce that by half.

CAPT. MONTGOMERY: Referring back to the proposed requirements for membership in the College, I invite attention to the wording of Section 1 (c): "If he is not a bona fide teacher or permanent laboratory worker, he shall have been in the actual practice of internal medicine at a permanent location for at least three years preceding nomination for Fellowship."

A strict reading of this might make it extremely difficult for any medical service officer. For instance, his residence is not permanent and is not of his own selection and the three years, if considered consecutive preceding nomination, might render his eligibility impossible.

DR. MIDDLETON: The Credentials Committee has not interpreted this regulation strictly in the past with regard to medical officers, for many from the Services have qualified. A correction might readily be included, however.

DR. MARTIN: How about the Veterans Bureau being included in those changes?

CHAIRMAN IRONS: That, too, should go in.

May we now have the report from the Committee on Fellowships and Awards, Dr. Francis Blake.

DR. BLAKE: The Committee on Awards received during the year 178 inquiries with respect to Clinical Fellowships. Of these, 51 bona fide applications were filed. Of these, five were withdrawn before Committee action. A preliminary screening reduced the number from 46 to 30 qualified applicants. Thirty were circulated to the Committee. Ten have been appointed as follows:

Dr. Joseph M. Barker, cardiology at the University of Michigan, from January 9, 1946—$3,000.00.

Norman L. Cressy, infectious diseases at Yale University, from February 1, 1946—$3,000.00.

John Franklin, internal medicine at Johns Hopkins Hospital, upon release from military service—$2,400.00.

John B. Hickam, circulation at Emory University, from June 1946—$2,500.00.

John S. Hunt, infectious diseases at Vanderbilt University, from April 1, 1946—$2,000.00.

Albert W. Lapin, Montreal, cardiology at the University of Michigan, Emory University, and Massachusetts General Hospital, from May 1, 1946—$1,800.00.

Gordon S. Myers, cardiology at Massachusetts General Hospital, from October 1, 1946—$2,400.00.

E. A. Rasberry, Jr., gastro-enterology at University of Pennsylvania, from July 1, 1946—$2,400.00.

Hugh Tatlock, clinical medicine at Yale University, from September 1, 1946—$3,000.00.

Philip A. Tumulty, internal medicine at Johns Hopkins Hospital, from January 1, 1946—$2,500.00.

That completes the appointment of Clinical Fellows and uses the $25,000 appropriated by the College for this purpose.

There have been 11 applications for Research Fellowships. One appointment was made at the December meeting, of Kenneth A. Evelyn, Montreal, to work with Dr. J. C. Meakins and Dr. C. Lyman Duff at the Royal Victoria Hospital. It is now recommended that two other candidates be awarded Research Fellowships by the College. The first of these is Charles P. Emerson, Jr., of Boston. He was

awarded a Research Fellowship just prior to the war but withdrew from it to enter the Army. He has now re-applied. He proposes to work at the Thorndike Memorial, Boston City Hospital, under the direction of Dr. George R. Minot and Dr. William B. Castle, from June 1, 1946—$2,500.00.

The second recommendation is that a Fellowship be awarded in research to Dr. Thomas S. Sappington, of New Haven, Connecticut. He is a graduate of Harvard Medical School, 1941. He has since that time had training at Yale and at the New Haven Hospital. He desires to work on nitrogen metabolism in the field of gastro-intestinal disease under the direction of Dr. H. L. Bockus at the Graduate Hospital of the University of Pennsylvania, Philadelphia, from October 1, 1946—$2,500.00.

That makes three Research Fellows at a stipend of $2,500.00 each, using $7,500 appropriated by the College for this purpose.

I would move approval of the recommendation of the Fellowship Committee for the appointment of Drs. Emerson and Sappington as Research Fellows. I also move approval of the appointment of the Clinical Fellows as read.

. . . The motion was seconded by Dr. Middleton and carried. . . .

CHAIRMAN IRONS: The next will be the report of the American Board of Internal Medicine, Dr. Reginald Fitz, Chairman.

DR. FITZ: We have had a successful year and have just completed examining a group of more than 200 men. The work of the Board has been carried on about the same as usual. We are facing practically a renovation of the Board at the beginning of the next fiscal year, July 1. You have already learned of the desirability of increasing the size of the Board. As far as we can determine from our Constitution, it is within the power of the Board to increase its membership. We obtained legal advice on that point. We would like to have seven members from the College and five members from the Section on Medicine of the American Medical Association. We understand that the Board of Regents of the College will make nominations at its meeting on Friday of this week and the Board of Internal Medicine will thereafter make the elections. The financial status of the Board is satisfactory.

CHAIRMAN IRONS: This report will be received. Dr. Clough, our Acting Editor, will kindly report.

DR. CLOUGH: As yet there has not been a meeting of the Committee on the ANNALS. I have very little that is new. So far as material is concerned, we are getting a larger number of articles submitted. Many of them are still not too good; probably less than half of those that have been submitted are accepted. Material to fill the June, July and part of the August issues has already gone to the printers and in addition we have twenty main articles accepted for publication and about ten more under consideration which are likely to be accepted. This would run us for a full three months period beyond August. That is about as large a backlog of articles as it is desirable to have under present conditions, because if we postpone publication too long, we get the reputation of holding up articles until they are stale. We have tried to give priority to certain articles that seem to be of current interest and importance.

We have an ample number of case reports for publication. Now that we have resumed the Annual Meetings, and shall obtain manuscripts of the papers there, we shall have an abundance of material from which to select.

In accordance with the advice of the Board of Regents, we did not accept the proposition to publish another number devoted wholly to medical-legal articles, but we have accepted about five individual articles, scattering them one at a time.

So far as promptness of publication is concerned, we have done as well as we could, with the exception of the Convention number which was held up for several days to get the complete program. Our manuscript material has been on time. There is still, however, substantial delay in printing so that most of the numbers have not appeared until very late in the month. I do not think there is anything that the

editor's office can do about that. Editorials, I think, are the most difficult problems there are to handle; if any members of the Board of Regents have ideas which they would like to incorporate in editorial form, they would be most welcome. We have not been able to get out book reviews satisfactorily as yet, but I think from now on there will be enough available men capable of reviewing a book to enable us to get out a reasonably large number. The only other thing that I planned to recommend to the Committee on the ANNALS relates to the salary of one of our secretaries who asked for a substantial increase. After consulting with the Executive Secretary of the College, we granted her temporarily an increase from $1440.00 per annum to $1800.00 per annum. I should recommend through the proper channels that eventually this be made permanent.

SECRETARY LOVELAND: The last matter has been placed on the agenda of the Finance Committee. The recommendation was absolutely necessary to keep Dr. Clough's work from being seriously interrupted.

Supplementing Dr. Clough's report, we are having far greater difficulties in getting adequate paper now than during the war. The printers have greater difficulty with labor in getting the ANNALS printed. It isn't the fault of the Acting Editor or of the printers; but the fault of current postwar conditions. We think we have one of the best printing establishments in the country but they are experiencing many difficulties.

We are experiencing difficulty in determining the quantity of the ANNALS to print. With the termination of the war and the eventual cancellation of Army and Navy orders for the ANNALS, we anticipated a slump in circulation. Quite the opposite is our experience. Subscriptions keep pouring in in unexpected numbers with the result that stock of past issues is promptly exhausted. From month to month we have been increasing the order to our printers, but with the shortage of paper, we naturally do not want large overruns. We believe by July the situation will be reasonably leveled so that we can more accurately estimate in advance the quantity required.

DR. CLOUGH: I believe Dr. Pincoffs will be able to resume the editorship within the relatively near future. It is only recently that he has been technically discharged from the Army.

CHAIRMAN IRONS: The ANNALS have profited under your able editorship very much, Dr. Clough, and we thank you.

Reports from other committees will be received at the next meeting of the Board of Regents.

. . . The Secretary read various announcements and the meeting was adjourned at 4:45 p.m. . . .

Attest: E. R. LOVELAND,
Executive Secretary

MAY 14, 1946

The second meeting of the Board of Regents during the Philadelphia Annual Session was held at Convention Hall, Tuesday, May 14, 1946, at 12 o'clock noon, with President Ernest E. Irons presiding, Mr. E. R. Loveland acting as Secretary, and with the following in attendance:

Drs. David P. Barr; James J. Waring; William D. Stroud; George Morris Piersol; T. Homer Coffen; Jonathan C. Meakins; Hugh J. Morgan; Francis G. Blake; James F. Churchill; Reginald Fitz; Roger I. Lee; Charles T. Stone; Walter B. Martin; James E. Paullin; LeRoy H. Sloan; George F. Strong; Paul W. Clough; Chauncey W. Dowden; C. C. Shaw, Educational Director; and, in addition, Rear Admiral George W. Calver (MC), USN, and Dr. William J. Kerr, a former President of the College, were present as guests.

The meeting was called to order by President Irons, the Secretary recorded the roll and presented a transcript of the minutes of the preceding meeting of the Board which, by common agreement, were not read in toto.

CHAIRMAN IRONS: Some weeks ago, Admiral Calver, of Washington, wrote asking to be allowed to present certain facts which he and his colleagues have developed with respect to the changes in the medical set-up in this country. Admiral Calver has brought with him certain documents and while I am sure we shall not have enough time to go into them very extensively, we shall be glad to listen to him in a brief discussion of the program, administratively.

. . . Admiral Calver presented, at some length and with appropriate discussion, various bills including S. 2143 and H.R. 3293 pending before the 79th Congress in the House of Representatives and the Senate of the United States, dealing with health service plans. His remarks and the plans and proposals were, by request, removed from the record. . . .

CHAIRMAN IRONS: Our first official report will be from the Board of Governors, Dr. Dowden, Chairman.

DR. DOWDEN: First of all, I want to refer to combined meetings of the Regents and Governors. One of the last things my predecessor, Dr. William Breed, did before he passed on, was to send a letter to each member of the Board of Governors asking for his reaction to the combined Regents and Governors meeting held therebefore in Chicago. I was much interested in the reports from the Board of Governors and the enthusiasm with which the various Governors answered that letter, and how anxious they were to have those meetings continued.

Dr. Edward L. Bortz has been elected Vice Chairman of the Board of Governors, that office having been vacant since I became Chairman automatically following the death of Dr. Breed.

The report from the Survey Committee was read by Dr. Lathrope, but the hour was drawing late, everyone was tired and it seemed very evident the report would be very far-reaching and that extemporaneous discussion would get us nowhere, so it was suggested that mimeographed copies of the report be sent to every Governor for study and then be discussed at the next meeting of the Board of Governors the following year before any report by the Governors can be made to the Board of Regents.

It was suggested that it would require two years at least to make the necessary changes if we waited a year to discuss it and another year to allow for the change. The motion finally put was that these reports be mimeographed and sent to each Governor and they should make their own comments after studying it thoroughly and send them to the Chairman who in turn would report to the Regents at its autumn 1946 meeting. There are two objections to that, as I see it. Much will be said by each Governor, but it is going to be rather difficult to crystallize and consolidate their opinions. It would be rather simple if we could have the whole discussion together and arrive at some common opinion. I, therefore, doubt if my report to you in the autumn will have great value. I hope the Board of Regents will not act upon this very important resolution until we have a chance for a combined meeting of the Governors and Regents. This matter is entirely too important to pass upon without a very careful study. It has to do with the future of the College and it deserves a great deal of thought and deliberation.

I have received numerous letters from time to time from members of the Board of Governors, but I am not going to take much of your time now for discussion. However, here is a short letter from Dr. Moffatt, of Montreal, who says, "There appears to be a considerable percentage of rejections for admission to Associateship. Do you not believe that if some grounds upon which these rejections are made are

better known to the Governors, without entering into personalities, that it would serve as a guide in selecting candidates?" Such matters are intimately connected with other things which should be discussed; they are intimately associated with this discussion of the proposals by the Survey Committee.

. . . On motion by Dr. Paullin, seconded by Dr. Fitz, and carried, it was RESOLVED that action on the report of the Survey Committee be deferred until after the Regents and Governors have received mimeographed copies thereof. There followed discussion of the possibility of having a joint meeting of the Governors and Regents during the current week and it was determined to have the report of the Survey Committee mimeographed immediately and to arrange a joint meeting of the Regents and Governors on Wednesday, May 15, at 12 o'clock noon. The Chairman of the Board of Governors, Dr. Dowden, pointed out that even by having a joint meeting on such short notice, it probably would not be feasible to take final action on such short notice, but that common discussion would clarify many points. . . .

CHAIRMAN IRONS: May we have the report of the Committee on Constitution and By-laws, Dr. Paullin, Chairman.

DR. PAULLIN: Mr. Chairman, the Committee on Constitution and By-laws offers an amendment to the By-laws, Article 4, Section 2, as an added paragraph:

"The members of the Board of Governors shall each serve for a term of three years and not more than two consecutive terms." From the minutes of the Board of Regents, the Committee was directed to prepare a proper By-law for the above and this amendment would be presented for adoption at the next Annual Business Meeting of the College. I move the adoption of this amendment.

DR. PIERSOL: I second the motion.

MEMBER: I am all for the change. The more we rotate the officers, the more men we will get into the fold.

MEMBER: Could a Governor be returned to the Board again later after serving two consecutive terms?

CHAIRMAN IRONS: A member could be off for awhile and then be returned to the Board.

MEMBER: Has the Board of Governors been asked about this? What is their reaction?

DR. DOWDEN: It was up for brief discussion yesterday, but it is particularly scheduled for discussion tomorrow. Thus far most of the sound thinkers on the Board have been very much opposed to this resolution. In the first place, it is believed that the men who have attained the greatest prominence as well as the greatest usefulness in and to the College, have come up by way of the Board of Governors. I could name a great many of them, but you know them yourselves; practically all of them were Governors for more than six years. Probably many of these men would have been ineligible for the higher offices at the end of the six year term, for they were just then reaching their period of greatest usefulness and influence. I do not think the term of Governors should be over 9 years, or 3 consecutive terms. I feel that you are penalizing the College, and while you will be getting rid of some of the older men, you are going to sacrifice some young men who are coming on a little later and who are going to be of great help to the College.

. . . There followed some general discussion in which members of the Board of Regents participated generally. There were some who felt that the new proposal should not be rushed through too quickly and others who felt that the recommendations should be modified to provide for a maximum of three consecutive terms of three years each. Furthermore, it was pointed out that if this By-law were adopted,

the Nominating Committee would have to revise its slate of nominations for Governors and that there would not be adequate time to do this in the midst of the General Business Meeting. It was also pointed out that the Board of Regents had originally been responsible for adopting a self-denying ordinance itself, limiting the terms of the Regents to two consecutive terms. Many thought that theoretically some limitation should be adopted to end criticism of the College being directed "by the same old crowd", and that younger men ought to be given an opportunity. On motion by a member, seconded and regularly carried, it was resolved that this resolution for the adoption of an amendment to the By-Laws, limiting tenure of Governors to two consecutive terms, be laid on the table. . . .

CHAIRMAN IRONS: Next we have the report of the Advisory Committee on Postgraduate Courses. Dr. Bortz, the Chairman, is not present, nor is the Educational Director, Dr. C. C. Shaw, and we are asking the Secretary, Mr. Loveland, to give a report in brief.

SECRETARY LOVELAND: Dr. Shaw had prepared a detailed report about the initiation of a program for the aid of veterans, the conferring of Fellowships and the conduct of our postgraduate course program. A part of this has already been covered by the report of Dr. Blake, Chairman of the Committee on Fellowships and Awards. In regard to our postgraduate courses, ten have been organized on our spring schedule and practically all of them have been over-subscribed. An outline of the courses is as follows:

No.	Dates	Title	Director	Institution
1	(three sections) A—March 4–9 B—April 8–13 C—July 8–13	Clinical Allergy	F. M. Rackemann	Mass. Gen. Hosp.
2	March 18–23	General Medicine	H. A. Reimann	Jefferson Medical College
3	March 25–30	General Medicine	Charles T. Stone	Univ. of Texas School of Medicine
4	April 1–19	Internal Medicine	James H. Means	Mass. Gen. Hosp.
5	June 3–8	Metabolism and Nutrition	Tom D. Spies	Hillman Hospital
6	April 22–27	General Medicine	James E. Paullin	Emory University School of Medicine
7	April 29–May 4	Gastro-enterology	Henry L. Bockus	Graduate Hospital
8	May 6–11	Cardiology	Wm. G. Leaman, Jr.	Woman's Medical College of Pa. and Philadelphia General Hospital
9	May 6–11	Thoracic Diseases	John Alexander	University of Michigan Medical School
10	June 17–28	Internal Medicine	Stacy R. Mettier	University of California

The majority of the registrants have been members of the College. A fair proportion, possibly one-third, were medical officers in the Armed Services or returning veterans. A comparatively small number of non-members could be accommodated because of limited facilities.

A program of 17 courses has been prepared for the autumn of 1946, but, due to

certain extenuating circumstances, the number will be reduced to 13, for which the schedule is as follows:

No.	Dates	Title	Director	Location
1	Sept. 2–14	Internal Medicine	R. R. Snowden	Pittsburgh, Pa.
2	Sept. 23–28	Psychosomatic Medicine	Franklin G. Ebaugh	Denver, Colo.
3	Oct. 7–19	Internal Medicine	Homer P. Rush	Portland, Ore.
4	Oct. 14–18	Clinical Neurology	Bernard Alpers	Philadelphia, Pa.
5	Oct. 21–26	Hematology	Charles A. Doan	Columbus, Ohio
6	Oct. 21 to Nov. 1	Internal Medicine	Wallace M. Yater	Washington, D. C.
7	Nov. 4–9	Allergy	Robert A. Cooke	New York, N. Y.
8	Nov. 4–9	Cardiology	Paul D. White	Boston, Mass.
9	Nov. 11–16	Gastro-enterology	Walter L. Palmer	Chicago, Ill.
10	Nov. 18–23	Internal Medicine	Joseph M. Hayman, Jr.	Cleveland, Ohio
11	Nov. 25 to Dec. 6	Internal Medicine	J. C. Meakins	Montreal, Que.
12	Dec. 2–7	Chemotherapy	W. Barry Wood, Jr.	St. Louis, Mo.
13	Dec. 2–7	Cardiology	Frank Wilson	Ann Arbor, Mich.

It is the purpose of the Advisory Committee on Postgraduate Courses to make these courses more substantial and fundamental, to limit the number of very short courses and to increase the number of courses of two, three or four weeks.

A matter that needs the approval of the Board of Regents is that of the fees charged for small clinical courses where the registration is very limited. This spring we had a series of three courses on clinical allergy, each limited to six registrants. Obviously, our own rates of tuition fees of $20.00 a week to members and $40.00 a week to non-members are totally inadequate for these small courses. The Committee on Postgraduate Courses and the Committee on Finance have been consulted and they are in agreement that we recommend to the Board of Regents that the tuition fees be increased to $40.00 and $80.00 for members and non-members, respectively, in the case of purely clinical courses where the registration is limited to 12 or less. One member of the Committee who approved it said he did so reluctantly and, therefore, it is felt that the Board of Regents should officially pass on this matter as a principle.

. . . A motion was made, seconded and regularly carried, approving the recommendation with regard to fees for restricted clinical courses with registration limited to 12 or less. . . .

SECRETARY LOVELAND: Another matter in connection with the postgraduate courses of the College is that Dr. C. C. Shaw, who has served as Educational Director since November 1, 1945, has tendered his resignation as of May 31, 1946, to accept another appointment. His resignation has already been accepted by the Executive Committee of the College, and the Secretary General, the President and the Executive Secretary were authorized to appoint a successor, not as Educational Director but as an Executive Assistant to the Executive Secretary. A number of candidates have been interviewed and we are ready to recommend the appointment of Mr. Frederick Pindar to this post on June 1, but he will be unable to devote his whole time to the College until September 1. Mr. Pindar has been thoroughly investigated. He has a fine record of training and experience, his most recent work being, for the past four or five years, the Assistant to Dr. A. N. Richards, Vice President of Medical Affairs of the University of Pennsylvania. Recommendations of the most acceptable type have been received from many men whom you will know, such as Dr. Richards, himself, Dr. O. H. Perry Pepper, and various administrative officers of the University and others.

. . . On motion, seconded and regularly carried, the action by the President, Secretary General and Executive Secretary in appointing Mr. Pindar was approved. . . .

CHAIRMAN IRONS: Is there a report from the Committee on Educational Policy, Dr. Lee, Chairman?

DR. LEE: The Committee has no formal report. I sat in at the meeting of the Advisory Committee on Postgraduate Courses; the discussion was purely general and it was recognized that the immediate conditions were very transient.

CHAIRMAN IRONS: May we have a further report from the Committee on Credentials now?

DR. PIERSOL: The Committee on Credentials held a special meeting yesterday at which all members were present. The Committee believes that it is necessary, in order to safeguard properly the interests of the College, that the present proposal form for admission be retained, amplified and changed as occasion arises to meet contemplated new requirements.

DR. DOWDEN: I move the report be adopted.

DR. PAULLIN: I second the motion.

CHAIRMAN IRONS: The matter is open for discussion. The Chairman would like to see this matter very carefully considered to avoid unfavorable discussion and the development of prejudice among people who do not understand the origin of the American College of Physicians.

. . . There followed general discussion with practically every member of the Board participating, many feeling that the advice and experience of the Credentials Committee should be followed, and an equal number recommending that questions on the proposal blank referring to race and religion be deleted. . . .

CHAIRMAN IRONS: May we have the report of the Committee on Public Relations, Dr. Lee, Chairman?

DR. LEE: The Committee on Public Relations met this morning. It recommends the adoption of the following resolution, which I move:

RESOLVED, that the Fellowship dues of Dr. Henry I. Shahon, Roxbury, Massachusetts, and Dr. Jacob Jesse Singer, Beverly Hills, California, be waived for 1946 and until their resumption of practice, this action due to present illness.

. . . The motion was seconded and passed. . . .

DR. LEE (Continuing): The Committee received two resignations and recommends the following:

RESOLVED, that the resignation of Dr. Newton Thomas Saxl, F.A.C.P., New York, New York, be accepted.

RESOLVED, that instead of accepting the resignation of Dr. John A. Wentworth, F.A.C.P., Hartford, Connecticut, he be retained on the Roster and his dues waived because of ill health, the waiver to continue until his recovery and resumption of work.

. . . Both motions were seconded and unanimously passed. . . .

. . . Dr. Lee, continuing his report, presented a disciplinary case, that of an Associate of the College against whom charges had been received, including conviction by the Federal Government as a result of income tax evasion and other unprofessional conduct. After careful review and discussion, a resolution was adopted, providing that formal charges be instituted and action be taken in accordance with provisions of the By-laws of the College. . . .

DR. LEE (Continuing the report of the Committee on Public Relations): The next item in our report refers to members to be dropped for delinquency in dues of two or more years time. Dr. ————————, F.A.C.P., Ukiah, California, is delinquent since January 1, 1944, and answers no communications. Dr. ————————, Woodhaven, New York, is likewise delinquent for more than two years.

The provisions of the By-laws make it incumbent upon the College to drop these two members from the Roster and the Committee recommends that their names be so dropped and I so move.

. . . The motion was seconded and carried. . . .

DR. LEE (Continuing): The Committee has a communication from Dr. Ernest C. Faust, Secretary of the American Academy of Tropical Medicine, requesting that the American College of Physicians join with various other organizations in sponsoring a meeting in 1947, or as soon as practicable, on the general subject of Tropical Medicine, and that the President of the College be empowered to appoint a member or representative. There will be no financial obligation. The proposed resolution is a long one, but the Committee can see no objections to it. The resolution is as follows:

"BE IT RESOLVED, that the American College of Physicians heartily endorse the proposal of the American Academy of Tropical Medicine that an international congress on tropical medicine and malaria be held in the United States at an early date, and that the American College of Physicians join with the American Academy of Tropical Medicine, in petitioning the State Department of the United States government to sponsor officially, and invite international participation in such a gathering at as early a date as is regarded as opportune, and direct the secretary of the American College of Physicians to formally advise the State Department of this endorsement.

"AND BE IT FURTHER RESOLVED, That the president of the American College of Physicians is authorized and empowered to appoint a Fellow of the American College of Physicians to represent the American College of Physicians on a committee composed of duly authorized and appointed representatives of the Association of American Physicians, American Public Health Association, American Academy of Tropical Medicine, American Society of Tropical Medicine, National Malaria Society, American Society of Parasitologists, Southern Medical Association, American Medical Association, American College of Physicians, American Association for the Advancement of Science, and the Section on Medical Science of the National Research Council, to meet on call from the president of the American Academy of Tropical Medicine, for organization, and in their organized capacity to assist the State Department in developing, promoting and holding such a congress, and the American College of Physicians will further give all practicable support to the realization of this project."

The Committee recommends that these resolutions be adopted by the Board of Regents, and I so move.

. . . The motion was seconded and passed and subsequently, President David P. Barr appointed Dr. Joseph M. Hayman, Jr., F.A.C.P., Cleveland, as the College representative. . . .

DR. LEE (Continuing): Referred business from the Board of Regents. At the last meeting of this Board, November 18, 1945, the Board of Regents referred to the Committee on Public Relations a consideration of whether to extend College membership beyond North America and its possessions. The present policy is to restrict membership to North American countries and their dependencies and, further, to physicians who speak or read English. The Secretary reports that the reason for this action was due to a feeling that a man who can neither speak nor read English would contribute little to the College and receive but little value from his College membership. He would seldom attend meetings or participate in College activities. The College has no machinery under its present By-laws whereby candidates from other countries can qualify. The Committee discussed this matter at length and voted that this referred business be continued and referred to this same Committee, or successor Committee, for further study and adoption. The Committee feels it is not now the time, probably, to adopt any change in the policy, but likely in the future there may be some change which would make this desirable. The Committee recommends

without prejudice that this item of business be continued on the agenda of the next Committee on Public Relations and I so move.

. . . The motion was seconded and carried. . . .

. . . Likewise, a motion to adopt the report as a whole was seconded and carried. . . .

CHAIRMAN IRONS: We will now have the report of the Committee on Finance by Dr. Lee, Chairman.

DR. LEE: The Finance Committee had a meeting at which the President of the College, the Executive Secretary and the Treasurer were present.

1. The financial status of the College seemed to be entirely satisfactory. The Executive Secretary reports that the income from the Technical Exhibits will more than cover the expenses of this meeting.

2. The final financial report of 1945 was published in the April 1946 issue of the ANNALS OF INTERNAL MEDICINE; likewise, the Auditor's official report. I move that the financial report as published and the Auditor's report be accepted.

. . . The motion was seconded and carried. . . .

DR. LEE (Continuing): There were various security transactions since the last meeting of this Board. Under the By-laws the Board of Regents should give specific approval to changes in the Endowment Fund and, therefore, I present the Endowment Fund changes.

Sales

ENDOWMENT FUND		*Cost*	*Sold For*	*Gain*
12- 6-45	5,000 Great Northern Railway, Gen. Mort., Series "B," 5 ½s, due 1952	$4,463.45	$6,060.00	$ 1,596.55
12- 6-45	5,000 Pennsylvania Railroad, Gen. Mort., Series "E," 4 ¼s, due 1984	5,013.10	6,385.00	1,371.90
1-29-46	50 Shares Johns-Manville Corp., common	4,789.55	7,220.80	2,431.25
				$ 5,399.70

Purchases

ENDOWMENT FUND		
1-29-46	80 Shares, Ingersoll Rand Co., common	$11,243.10
1-29-46	7,000 United States of America Savings Bonds, Series "G," 2 ½s, due 1958	7,000.00
2-20-46	100 Shares, Houston Light & Power Co., common	8,837.80
4-25-46	6,000 American Tobacco Co., 3s, due 1969	6,375.00
4-27-46	50 Shares, American Smelting & Refining, 7%, Pfd.	9,517.80

These transactions have already taken place and I move they be approved by the Board of Regents.

. . . The motion was seconded and carried. . . .

DR. LEE (Continuing): There are also other transactions for the General Fund which I am now reporting for your information.

Sales

GENERAL FUND		*Cost*	*Sold For*	*Gain*
12- 6-45	5,000 Chicago, Burlington & Quincy R. R. Co., Gen., 4s, due 1958	$4,893.75	$5,897.50	$ 1,003.75
12-28-45	100 Shares, Curtiss-Wright Corp., Class A	2,652.80	2,776.08	123.28
				$ 1,127.03

Purchases

GENERAL FUND

2– 7–46 50 Shares, Continental Can, 3 ¾s, Pfd. ..... $ 5,601.75

It is also contemplated that the following securities shall be purchased from the cash receipts at the present time. One-half the bonds of the Oregon-Washington Railroad will be purchased for the Endowment Fund account.

Security	Annual Dividend	Approximate Current Market	Yield	Cash Value	Annual Cash Income
SUGGESTED PURCHASES					
$10,000 OREGON-WASHINGTON RAILROAD & NAV. First 3s, 10/1/60 (Call. @ 104 1/2; for S.F. @ 102 1/4)		105 3/4	2.53%	$10,575	$300
200 shs. COMMONWEALTH EDISON Co., Common	$1.40	36	3.89	7,200	280
100 shs. PHILADELPHIA ELECTRIC Co., Common	1.20	30	4.00	3,000	120
				$20,775	$700

I move the approval of the Board of Regents for these purchases, specific with regard to the Endowment Fund item.

. . . The motion was seconded and carried. . . .

DR. LEE (Continuing): Additions required to the 1946 Budget:

. . . By individual resolutions, the following additions to the 1946 budgets were approved, after detailed review by Dr. Lee:

$ 300.00 Editor's Office
1,150.00 Educational Director's Office (deficit to June 1)
2,500.00 Executive Secretary's Office.

. . . By resolution, the report of the Finance Committee was approved as a whole. . . .

CHAIRMAN IRONS: The Treasurer will not make a report at this time because he feels that the Finance Committee has adequately covered all that he would have to report. The next item is an announcement about exhibits.

SECRETARY LOVELAND: I just want to ask that members of the Board of Regents, if they have time, go through our Technical Exhibits. I am dependent upon advice from our Committee on Exhibits, Drs. Piersol, Wolferth and Klein. Our exhibits are selected carefully. We want your interest and advice. The exhibits produce a considerable income, about $21,000.00 this year. You will see nothing in our exhibit that is so commonly seen at the exhibits of other medical societies. We accept nothing that is irrelevant to the practice of medicine. There are no cigarettes, soft drinks, bananas and all sorts of irrelevant items displayed at many other meetings. We try to keep our exhibit on a high plane in every regard. We have published a bulletin about the exhibits which is distributed to every registrant. I would like to have your interest in the exhibits because we have a long range program. Furthermore, your interest as Regents of the College will mean much to the exhibitors.

. . . The meeting by resolution was adjourned. . . .

Attest: E. R. LOVELAND
Executive Secretary

MAY 17, 1946

The third meeting of the Board of Regents during the Philadelphia Annual Session convened in Room 101, Philadelphia Convention Hall at 12:40 p.m., Dr. David P. Barr, the new President, presiding and Mr. E. R. Loveland acting as Secretary. The following were present:

David P. Barr	President
Hugh J. Morgan	President-Elect
James J. Waring	First Vice President
A. B. Brower	Second Vice President
T. Homer Coffen	Third Vice President
William D. Stroud	
George Morris Piersol	
Francis G. Blake	
James F. Churchill	
Charles T. Stone	
Walter B. Martin	
LeRoy H. Sloan	
George F. Strong	
Ernest E. Irons	
T. Grier Miller	
Charles F. Moffatt	
Chauncey W. Dowden	Chairman, Board of Governors

PRESIDENT DAVID P. BARR: It is a pleasure to welcome to this Board Dr. Charles F. Moffatt, Dr. William S. McCann and Dr. T. Grier Miller.

For the first business of the day, we wish to discuss the meeting place for next year, and I will ask the Executive Secretary to present invitations.

SECRETARY E. R. LOVELAND: We do not have the usual quantity of invitations, but it will not be necessary to read all of the letters. We have formal invitations from St. Louis and from Chicago, supported by letters from the local medical societies and other agencies. It is obvious that we should discuss these two invitations, because it is assumed that our next meeting should be held westward, for it has been our custom to alternate between the east and middle west. These two invitations are official and they are complete.

MEMBER: I would like to say a word for St. Louis. I know the standard of clinic and clinical facility arrangements would be adequate. In talking with the Convention Bureau there, however, it appears that St. Louis, at the present time, is not able to offer a sufficient number of hotel rooms. Recently St. Louis entertained the Association for the Advancement of Science. I was interested to hear from the Convention Bureau on that, and they told me they accommodated 2,500 people, but they explained that they doubled them up three or four in a room, and they do not feel that they could treat members of the American College of Physicians that way. I feel it is not feasible to consider St. Louis for next year.

DR. LEROY H. SLOAN: Mr. Chairman, in consultation with the Convention Bureau and hotels of Chicago we have found that, at particular times, Chicago seems to be perfectly ideal. We have been assured that Chicago will furnish an adequate number of rooms for our members and guests. The Chicago Convention Bureau assumes full responsibility and has sent a representative here to talk about their facilities and to answer questions.

We contacted the dean of every medical school and college, the superintendent or medical director of each hospital, and others that were particularly interested in this

Convention. We have received a reply from every one to whom a letter was sent, heartily welcoming us and promising to do everything to make the meeting a success.

PRESIDENT BARR: May we have a report from the Chicago Convention Bureau?

MR. FRANK POWER (Chicago Convention Bureau): We can accommodate you with 2,000 to 2,500 rooms, if necessary. I represent the Convention Bureau and the hotels as a whole. It is our plan to have one centrally located hotel in Chicago as headquarters, and I shall attempt to place all of your members and guests in two or three hotels within a block or so from the headquarters hotel. I am thinking of the Palmer House, the Stevens Hotel and the Congress Hotel. Regardless of what hotel is specified as headquarters, there are many people who prefer to stay at their favorite hotel when in Chicago. We can furnish you with as much, if not more, in the way of facilities than any other city might offer. We will satisfy you in every way possible.

. . . There followed general discussion and considerations about local transportation facilities, clinic and hotel facilities and charges made by hotels for meeting room space. Mr. Power was of the opinion that no charge would be made for meeting space in Chicago. . . .

PRESIDENT BARR: If there are no further questions, we will call for action on the invitation from Chicago.

. . . Upon motion duly made, seconded and carried, Chicago was selected for the 1947 Annual Session. A further resolution was adopted directing that the meeting be held during the latter part of April, but leaving the fixing of final dates to the President, General Chairman and Executive Secretary. . . .

MEMBER: Mr. Chairman, as a suggestion the College meeting might be held the week preceding the meeting of the Association of American Physicians at Atlantic City. Many members come from the western States and if we could arrange the College meeting just preceding the meeting of the Association, it would facilitate matters, allowing our western members to come on east to the Association meeting without first returning home.

. . . A resolution was adopted appointing Dr. LeRoy H. Sloan as General Chairman of the Chicago Session. . . .

PRESIDENT BARR: We must elect a Secretary-General and a Treasurer of the College for 1946–47.

. . . Dr. George Morris Piersol was nominated, seconded and his reëlection unanimously approved by resolution. . . .

MEMBER: Mr. President, in passing this resolution I think we ought at the same time to express our very deep appreciation for the wonderful things Dr. Piersol has done for the College for so long a time. There are no words that I can say that would express our gratitude to him. (Applause.)

DR. GEORGE MORRIS PIERSOL: I want to express my gratitude for the confidence placed in me. However, we cannot escape the fact that the time will come when some one else should take over the Secretary-Generalship. As age creeps up, one's ability slows down; secondly, the general principle of having a perennial officer is not a good one for the organization. I want to tell you now, deeply as I appreciate the way in which you have coöperated with me over all these years, I think you should seriously consider the possibility and wisdom of replacing the Secretary-General with a younger and more vigorous man.

PRESIDENT BARR: May we have nominations for the office of Treasurer for 1946–47?

. . . Dr. William D. Stroud was nominated for reëlection. Nominations were closed, and he was declared, by resolution, reëlected as Treasurer of the College. . . .

. . . President Barr proceeded with the election of the Executive Committee and the appointment of other Committees as follows:

Executive Committee

David P. Barr, New York, N. Y., Chairman
Hugh J. Morgan, Nashville, Tenn.
George Morris Piersol, Philadelphia, Pa.
William D. Stroud, Philadelphia, Pa.
Francis G. Blake, New Haven, Conn.
James F. Churchill, San Diego, Calif.
Chauncey W. Dowden, Louisville, Ky.
Ernest E. Irons, Chicago, Ill.
James E. Paullin, Atlanta, Ga.

Committee on Advertisements and Commercial Exhibits

George Morris Piersol, Philadelphia, Pa., Chairman
Thomas Klein, Philadelphia, Pa.
Charles C. Wolferth, Philadelphia, Pa.

Committee on the Annals of Internal Medicine

Reginald Fitz, Boston, Mass., Chairman—1947
Walter B. Martin, Norfolk, Va. —1948 (filling out term of W. W. Palmer)
T. Grier Miller, Philadelphia, Pa. —1949

Committee on Constitution and By-Laws

James E. Paullin, Atlanta, Ga., Chairman —1948
Charles F. Moffatt, Montreal, Que., Canada —1949
George F. Strong, Vancouver, B. C., Canada—1947

Committee on Credentials

George Morris Piersol, Philadelphia, Pa., Chairman—1948
LeRoy H. Sloan, Chicago, Ill. —1947
A. B. Brower, Dayton, Ohio —1949
} From the Board of Regents

J. Edwin Wood, Jr., University, Va. —1948
*George H. Lathrope, Newark, N. J. —1947
Wallace M. Yater, Washington, D. C. —1949
} From the Board of Governors

Committee on Educational Policy

William S. Middleton, Madison, Wis., Chairman
Francis G. Blake, New Haven, Conn.
Hugh J. Morgan, Nashville, Tenn.

Advisory Committee on Postgraduate Courses

(Appointees of the Board of Governors)
Edward L. Bortz, Philadelphia, Pa., Chairman
Edgar V. Allen, Rochester, Minn.
Turner Z. Cason, Jacksonville, Fla.
Ernest H. Falconer, San Francisco, Calif.
James J. Waring, Denver, Colo.

Committee on Fellowships and Awards

Reginald Fitz, Boston, Mass., Chairman
T. Homer Coffen, Portland, Ore.

* Appointed by Board of Governors to complete term of J. Owsley Manier, resigned.

William S. McCann, Rochester, N. Y.
Hugh J. Morgan, Nashville, Tenn.
James J. Waring, Denver, Colo.

Committee on Finance
Charles F. Tenney, New York, N. Y., Chairman—1948
Roger I. Lee, Boston, Mass. —1947
Charles T. Stone, Galveston, Tex. —1949

Committee on Nominations
James J. Waring, Denver, Colo., Chairman —Regent
George F. Strong, Vancouver, B. C., Canada—Regent

Ralph A. Kinsella, St. Louis, Mo. —Governor
Asa L. Lincoln, New York, N. Y. —Governor

Jonathan C. Meakins, Montreal, Que., Canada—Fellow-at-Large

Committee on Public Relations
Roger I. Lee, Boston, Mass., Chairman —1947
Ernest E. Irons, Chicago, Ill. —1950
James E. Paullin, Atlanta, Ga. —1949
George F. Strong, Vancouver, B. C., Can.—1948
David P. Barr, New York, N. Y. —Ex Officio

Committee on Post-War Planning for Medical Service
George Morris Piersol, Philadelphia, Pa., Chairman
Edward L. Bortz, Philadelphia, Pa.
Ernest E. Irons, Chicago, Ill.
LeRoy H. Sloan, Chicago, Ill.

PRESIDENT BARR: We have had no recent information regarding the Committee on Post-War Planning for Medical Service, of which Dr. Piersol is the Chairman. Is it an active Committee?

DR. PIERSOL: That Committee is a group representing the College on the Central National Committee, which meets almost monthly in Chicago. Many groups are represented on the Central Committee. It is still in existence.

DR. ERNEST E. IRONS: I, with Dr. Piersol, have represented the College at several meetings of that Committee. The development of more activity is quite the feeling among most of those organizations represented. I think our College might very well be continued, perhaps in a little different form, on this Post-War Medical Committee, because it will be very helpful at our next meeting. This Central Committee is a sort of clearing house and a very important front for all medicine. It has been gratifying to see the amount of coöperation that has been obtained among these different organizations. The Committee has had, as a rule, twenty to thirty members in attendance, and I have been amazed at the desire and willingness of these people to come from all over the country. We have all kinds of problems with which to deal.

PRESIDENT BARR: We shall continue the Committee with Dr. Piersol as Chairman, and I may later appoint another member to take Dr. Walter W. Palmer's place, for he is no longer a member of this Board.

Conference Committee on Graduate Training in Medicine
Reginald Fitz, Boston, Mass., Chairman
LeRoy H. Sloan, Chicago, Ill.

Consulting Committee on Annual Sessions
David P. Barr, New York, N. Y., Chairman
LeRoy H. Sloan, Chicago, Ill.
Ernest E. Irons, Chicago, Ill.
George Morris Piersol, Philadelphia, Pa.
James E. Paullin, Atlanta, Ga.

Council for Study, Prevention and Treatment of Rheumatic Fever
Hugh J. Morgan, Nashville, Tenn.
William D. Stroud, Philadelphia, Pa.

PRESIDENT BARR: I should like to ask about the Council for Study, Prevention and Treatment of Rheumatic Fever, which was formed as a result of a resolution to appoint two representatives and to appropriate a fund of $1,000.00 by the College.

DR. HUGH J. MORGAN: I attended, as the representative of the College, a meeting of this so-called Council on Rheumatic Fever, which was sponsored by the American Heart Association. I am sorry to say I have no report to make, other than to state that the meeting was called to make plans to obtain funds, which would be made available for research on rheumatic fever.

PRESIDENT BARR: We will leave this Committee on the books, but we shall expect a report on it at the next meeting of this Board.

House Committee
William D. Stroud, Philadelphia, Pa., Chairman
T. Grier Miller, Philadelphia, Pa.
Charles L. Brown, Philadelphia, Pa.

Survey Committee

William S. Middleton, Madison, Wis., Chairman James E. Paullin, Atlanta, Ga.	From the Board of Regents
George Morris Piersol, Philadelphia, Pa. Wallace M. Yater, Washington, D. C.	From the Committee on Credentials
George H. Lathrope, Newark, N. J.	From the Board of Governors

American Board of Internal Medicine—In accordance with the report from the Chairman of the American Board of Internal Medicine, the Board of Regents nominated the following Fellows as representatives, three of whom shall be elected by the American Board of Internal Medicine and their names and terms of office later reported back to the College:

Alexander M. Burgess, Providence, R. I.
Richard A. Kern, Philadelphia, Pa.
William B. Porter, Richmond, Va.
Roy W. Scott, Cleveland, Ohio
Wallace M. Yater, Washington, D. C.

. . . The above elections are occasioned by the expiration of the term of one of the present ACP representatives on the American Board of Internal Medicine and the appointment of two additional members, bringing the total personnel of the Board up to twelve—five of whom will be representatives of the Section on the Practice of Medicine of the American Medical Association and seven of whom will be representatives of the American College of Physicians.

PRESIDENT BARR: Is there any new business?

SECRETARY LOVELAND: Mr. Chairman, a matter has been called to my attention that I would like to mention now concerning our future Annual Business Meetings.

Arranged at the end of the scientific session on Thursday afternoons, they are attended by a small number of Fellows, with the result that a comparatively small number participate in the administration of the College and the selection of its Officers. One of our new Regents made a very practical suggestion, namely, that the Annual Business Meeting be held during an extended intermission in the middle of the Thursday afternoon general session. This would insure an adequate attendance and, obviously, create a wider interest in the meeting.

DR. GEORGE F. STRONG: At the last meeting of the Board of Regents the matter concerning tenure of office of Governors was tabled. I would now like to move that we take it off the table, so that we may reconsider it. I so move, Mr. Chairman.

. . . The motion was seconded and carried. . . .

DR. STRONG: Mr. Chairman, I have spoken to a number of Governors about this matter. The consensus of opinion among them is that there should be some limitation of the tenure of office. I would now like to move that our previous resolution be altered from two consecutive terms to three consecutive terms of three years each.

DR. CHAUNCEY W. DOWDEN: I second the motion.

DR. JAMES J. WARING: Care should be taken to cover the fact that a good many of the members of the Board of Governors have already served two, three, four, or more, terms. Is this motion made for the purpose of allowing them to serve one more term after their present term? There should be a clear understanding of just when this rule will go into effect.

DR. STRONG: My interpretation would be that if this passes, when a man comes up for reëlection in the future, if he has served nine consecutive years, he is not eligible for reëlection.

PRESIDENT BARR: Probably about one-third of the Governors would be affected.

DR. MORGAN: I think it would be helpful to a new Governor coming into office if he had a year's experience, or at least one Annual Meeting, prior to his taking over the responsibility of Governor.

DR. STRONG: My supplementary thought back of my motion is that the matter be referred back to the Committee on Constitution and By-laws, with directions that they prepare a proper amendment providing limitation of office of Governors to three consecutive terms, so that formal action can be taken at the next meeting of the Board of Regents.

. . . The motion was put to vote and unanimously carried. . . .

. . . Upon motion duly made, seconded and carried, the meeting adjourned at 1:40 p.m. . . .

Attest: E. R. LOVELAND,
Executive Secretary

OBITUARIES

DR. CLYDE WALLACE KIRKLAND

Clyde Wallace Kirkland, Ph.B., M.D., Associate of the College by virtue of membership in the old American Congress on Internal Medicine, Bellaire, Ohio, died March 25, 1946, of coronary occlusion; aged 64.

Dr. Kirkland had been Secretary-Treasurer of the Belmont County Medical Society and President of the Board of Trustees of the Belmont County Tuberculosis Sanatorium. He was formerly councillor of the Seventh District of the Ohio State Medical Association and President of the Ohio Public Health Association, 1923–1924. More recently, he served on the staff of the Bellaire City Hospital, where he died.

DR. GROVE P. M. CURRY

Dr. Grove Price Mitchell Curry, an Associate of the American College of Physicians by virtue of membership in the former American Congress on Internal Medicine, Mount Kisco, N. Y., died during May, 1946. He was born in 1866 and thus lived to the age of eighty. In his last communication to the College he said, "It is getting near the sailing time. Life's pilgrimage has no time table."

Dr. Curry received his medical education at New York University Medical College, graduating in 1892. For a great many years he was a member of the staff of the Northern West Chester Hospital. He was a member of the American Public Health Association, the American Medical Association and a Fellow of the New York Academy of Medicine.